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Studies on the Convulsive Mechanism in Idiopathic Hypoparathyroidism[1]

[Hypoparathyroid Convulsions]

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THE LACK OF AGREEMENT not infrequently observed between the level of serum calcium and the occurrence of generalized convulsions in the 'low-calcium' types of tetany indicates the need for further information regarding other factors involved in the convulsive mechanism in such disorders. That a disturbance in the metabolism of calcium and phosphorus is primarily responsible for the initial development of the neuromuscular hyperexcitability characterizing parathyreoprivic tetany, as well as tetany associated with calcium deprivation or vitamin D deficiency, can no longer be gainsaid. Neither the milder symptoms of active tetany nor generalized convulsions occur in these clinical disorders without a marked decrease in the calcium of the blood plasma and other extracellular body fluids. Furthermore, all available evidence indicates that the ionized fraction of the calcium plays the chief rôle in this respect. That occurring in the combined or undissociated phase (either with protein or as colloidal calcium phosphate) appears to be physiologically inactive. The parathyroid glands have been shown to play a decisive rôle in the regulation of the Ca^{++} concentration (1, 2). In hypoparathyroidism the Ca^{++} is below normal; in hyperparathyroidism, it is above.

That diminution in the Ca^{++} concentration does not alone afford an adequate explanation for the various manifestations of active tetany is apparent from a number of considerations. For instance, while the signs of active tetany can be induced in subjects who are in a state of latent tetany by certain procedures known to decrease Ca^{++} concentration (e.g., hyperventilation of the lungs or excessive administration of alkaline salts), attempts to demonstrate a significant swing in the acid-base equilibrium toward the alkaline side just prior to the onset of spontaneous convulsions have so far failed. Alkalosis *per se* tends to increase neuromuscular hyperexcitability, even in the case of the normal subject; acidosis has the opposite effect. It is difficult to believe that the effects in this instance are dependent alone upon changes in the Ca^{++} concentration. McLean, Barnes and Hastings (2), confirming the conclusions of Collip (1) state: "It now appears, from the studies reported here and previously, that the Ca^{++} concentration in the plasma can be considered to be only one of the variables concerned in the symptoms of hypoparathyroidism, and presumably of hyperparathyroidism. The hypothesis that other factors, such as acid and alkali,

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known to influence the incidence or course of tetany, act solely by influencing the ionization of calcium in the plasma, appears to be no longer tenable." It has repeatedly been observed (3, 4, 5) that parathyroidectomized animals showing signs of active tetany and convulsions during the early postoperative days may later become entirely free from such manifestation by virtue of some unknown mechanism of adjustment, not necessarily involving changes in the serum calcium, inorganic phosphorus, protein or hydrogen ion concentration. Patients with postoperative or idiopathic hypoparathyroidism not infrequently show similar periods of freedom from symptoms, while these constituents of the serum remain the same as during periods of active tetany. The data included in the present report amply confirm this observation. Intercurrent acute infections frequently precipitate convulsive seizures in subjects suffering from latent tetany without necessarily altering the acid-base balance or the levels of serum calcium, protein or inorganic phosphorus. In fact, the latter constituent is often decreased during the course of an acute infection, particularly pneumonia, (6) instead of being increased as it tends to be inactive tetany.

These general observations suffice to emphasize the importance of obtaining more experimental data pertaining to other factors than calcium ion concentration that may contribute to the occurrence of generalized convulsions in the types of tetany under consideration. Such data would probably be helpful, also, in the elucidation of the convulsive mechanism in those forms of tetany due to excessive loss of gastric fluids, to hyperventilation of the lungs or to excessive ingestion of alkali. The present study, concerning the effects of certain procedures on the convulsive activity of a patient with idiopathic hypoparathyroidism, was undertaken with the object of securing further information on this phase of the problem.

CASE HISTORY

L.W., a white boy aged 15 years, was admitted to the Pediatric Service of the University of Minnesota Hospital with the complaint of pains in the muscles and generalized convulsions.

Present illness. He had had 'choking' attacks with difficulty in breathing at irregular intervals during the previous 2 years. Throughout this time, it had been assumed by his physician that he was suffering from idiopathic epilepsy because of the recurring generalized convulsions. For one year he had suffered, also, from spells of stiffness and cramping pains in the muscles of his hands, arms and legs. His voice was harsh during attacks. He complained that he was "jumpy" when touched. Attacks were usually associated with acute infections. His mother volunteered that he seemed to drink a great deal of water and tea.

Past history. Diseases: repeated attacks of pneumonia; measles and mumps several years before the onset of the present illness. There had been no injuries or operations and no family history of convulsive disorders or of other nervous disease. Diet: much fruit and starchy vegetables; very little milk, cheese or meat; some eggs; much bread and butter.

Physical examination showed a somewhat dwarfed white boy, whose height was 61 inches and weight 106 pounds. His skin was clear except for mild acne vulgaris of face and shoulders; color good. The thyroid gland was not palpable. Lymph glands and tonsils were small. Teeth were discolored and showed enamel defect of the incisors. There were no signs of cardiac or pulmonary disease. Blood pressure: systolic 115, diastolic 75 mm. of mercury. The abdomen and genitalia were normal. Neurological examination revealed nothing abnormal except general increase in neuro-muscular excitability. The Chvostek and Trouseau signs were strongly positive. Carpopedal spasms were readily induced by voluntary hyperventilation of the lungs.

Laboratory findings. X-ray of skull and long bones showed nothing abnormal. Routine urine analysis gave normal findings. Blood counts were normal. *Blood chemical data:* hemoglobin 14.9 gm. per 100 cc.; glucose (fasting) 82 mg. per 100 cc.; plasma cholesterol 252 and lecithin 162 mg. per 100 cc.; phosphatase activity 3.2 U; non-protein nitrogen 39.9 mg. per 100 cc.; serum albumin, 3.55 and serum globulin 3.51%; serum electrolytes: calcium 6.8, inorganic phosphorus 7.6, magnesium 0.89, sodium 324, potassium 17.8 and choloride 334 mg. per 100 cc.; Wassermann test negative. *Spinal fluid:* clear; no increase in pressure; 3 cells per cu. mm.; globulin negative; Wassermann test negative; calcium 3.9 and inorganic phosphorus 2.6 mg. per 100 cc.

PROCEDURES AND MATERIALS USED

The general plan of study was that of determining the effects on convulsive reactivity of such factors as: *a*), forced water retention with dilution of the extracellular body fluids (sustained post-pituitary antidiuresis); *b*), intravenous administration of typhoid vaccine (simulating acute bacterial infection; *c*), artificially induced fever (diathermy); *d*), water restriction; and *e*), voluntary hyperventilation of the lungs. The various tests were carried out in regular succession over a period of several months with short control periods interspersed between individual experiments. Since the mineral (particularly the calcium) content of the patient's regular diet prior to admission had been unusually low, it was decided to employ a similar low-mineral diet of known composition during the first phase of the study. The major experiments were later repeated while he was taking a diet furnishing approximately the same amounts of protein, fat, carbohydrate, water and vitamins but containing in addition standard or 'adequate' amounts of the various minerals.[2] The ratio of calcium to phosphorus

[2] The diet throughout the entire period of investigation contained protein 64, fat 124 and carbohydrate 224 gm. per day, supplemented by fresh lemon juice, yeast and cod liver oil to furnish required vitamins. Intake of the various mineral elements is shown in figure 1.

in the latter diet was approximately 1:1. The effect of parathyroid gland extract[3] on the response of the patient to pitressin[4] was also determined during the period of low mineral intake. The effect of giving cium, inorganic phosphorus, magnesium and other electrolytes, were measured in connection with each major experiment. The chemical methods used were those referred to in other reports from this clinic (7).

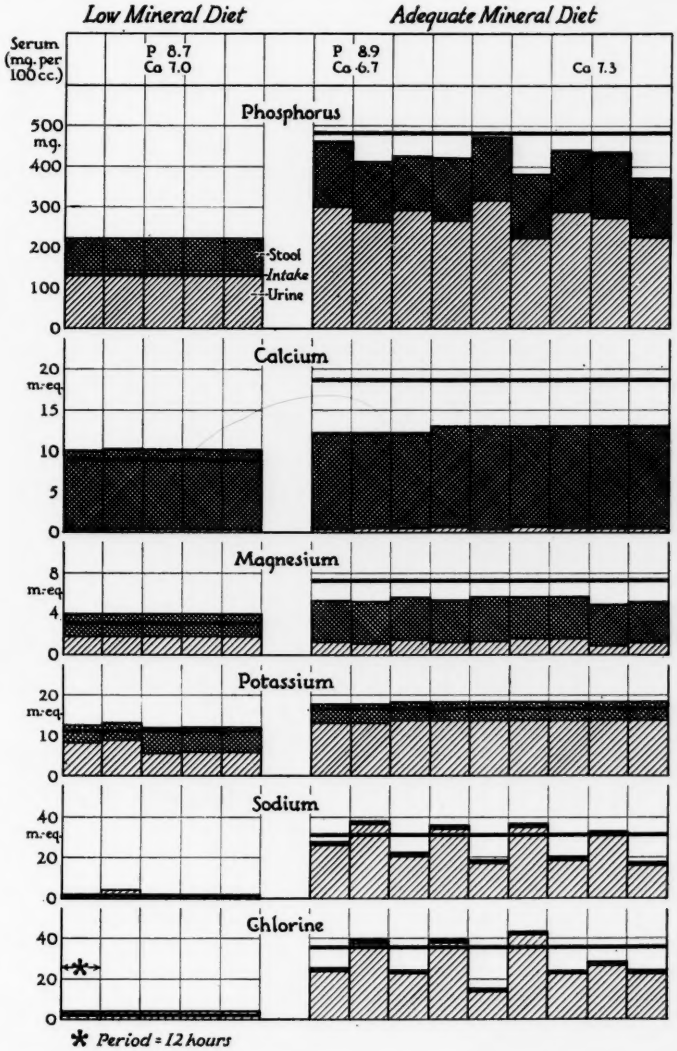

Fig. 1. Representative data pertaining to mineral exchanges during periods of low mineral intake and of adequate mineral intake. Intake indicated by heavy horizontal lines.

sufficient NaCl to prevent dilution of the extracellular body fluids during a period of post-pituitary extract (pitressin) administration was likewise determined. The total water balance and the individual mineral balances, as well as the serum protein, cal-

[3] Parathormone, Eli Lilly and Co., Indianapolis, Indiana.
[4] Parke, Davis & Co., Detroit, Michigan.

RESULTS

Representative results are presented graphically in the accompanying figures.

Mineral balances. Figure 1 shows true samples of data on the intake and excretion of the most significant minerals during the period of low-mineral intake as contrasted with that of 'adequate' intake and also

values for the calcium and inorganic phosphorus of the blood serum. Partition between the output by way of the stool and that by way of the urine is indicated but appears to be of no special significance. The most obvious difference between the data of the two periods is that pertaining to the nature of the mineral balance. While there was storage of calcium, magnesium and phosphorus in significant amounts during the period of higher intake, these same elements showed a definite negative balance during the period of low intake. Potassium appears to have shown a slightly negative balance during both periods, while sodium and chloride showed a slightly positive balance during the period of greater intake.

Although the patient had been on the diet in each instance for a period of at least one week before the mineral balances were determined and at least two weeks prior to the periods represented in the figure, no definite changes in the serum phosphorus and calcium resulted. A much more prolonged period on the low-calcium diet was later observed to reduce the level of serum calcium slightly.

Effect of low-mineral intake. For the sake of brevity results of a series of experiments, conducted while the subject was maintained on the low-mineral regimen, are presented in graphic form in figure 2.

In the light of the finding by Ellis (8) of an increased water content of brain tissue in experimental tetania parathyreopriva and the similar finding by Baar (9) in subjects with infantile tetany, it was thought desirable to determine the effect of sustained pituitary antidiuresis, which causes a retention of water and dilution of extracellular body fluids when the water intake is comparatively high and the mineral intake low. The latter condition presumably induces a shift of water across cell boundaries into the cells, including those of the nervous system. There is some evidence in favor of the assumption that electrolyte shifts likewise take place at the same time. Convulsions can be induced in a high percentage of epileptic subjects by this procedure (10).

It can be seen from the first panel of the chart (fig. 2) that carpopedal spasm developed and a generalized convulsion occurred as a result of the pitressin test. Before the latter was begun the patient was in a state of latent tetany, showing no outward signs. With continuous storage of water in the body, as indicated by a steady weight gain, the patient became conscious of 'tightening' and cramp-like sensations in his muscles and increased roughness of his voice. When the net gain in weight had reached approximately 4 per cent of the original body weight, the convulsion occurred without any measurable change in the total calcium or inorganic phosphorus of the

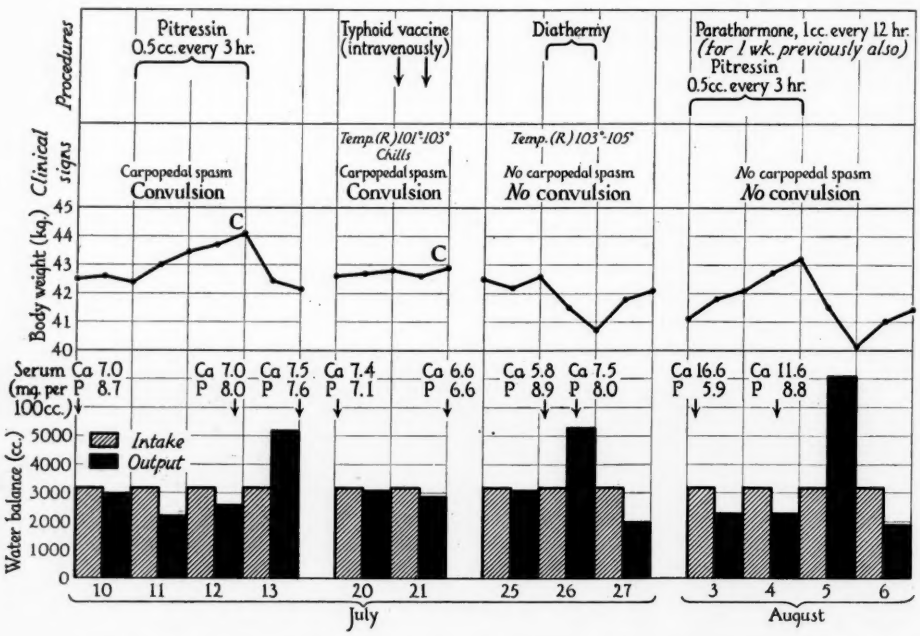

Fig. 2. Influence of low mineral diet on convulsive reactivity. (For explanation see text.)

serum. The total serum protein just before the experiment was begun was 6.45 per cent. Precisely the same value was obtained shortly before the convulsion occurred. Repetition of this experiment on a later occasion gave almost identical results with the convulsion occurring before marked signs of active tetany were observed.

The second experiment of the series, performed one week after conclusion of the first, was undertaken with the hope of determining the nature of the changes in body state which might explain the convulsant effect of acute infections in tetany. Intravenous administration of killed typhoid bacilli in febrile doses was considered to be the safest and otherwise most suitable substitute for a genuine acute infection.

It will be seen that carpopedal spasm developed as an accompaniment of the artificially induced chills and fever and that the subject had a generalized convulsion at the height of the fever following the second injection of vaccine. There was a small retention of water which was of doubtful significance. The serum calcium and phosphorus both showed slight decreases. These changes may or may not have played a rôle in the occurrence of the convulsion. That this incidental decrease of 0.8 mg. per 100 cc. in the serum calcium was probably not of paramount importance, however, was indicated by the finding five days subsequently of a value 0.8 mg. per 100 cc. lower, still without manifestations of tetany or recurrence of convulsive seizures.

In order to determine the effects of fever *per se*, artificial hyperthermia was produced by diathermy. The experiment referred to is presented in the third section of figure 2. Although the elevation of the rectal temperature exceeded that produced by the intravenous administration of typhoid vaccine by two degrees, no signs of tetany became manifest and no convulsion was thereby induced. The most striking physiological effect was the loss of body water from excessive sweating, as indicated by the weight loss shown in the chart. The serum calcium showed a significant increase, while the inorganic phosphorus showed a slight decrease. The total serum protein was elevated from 5.83 to 6.35 per cent at the same time. This change and the rise in calcium, along with other signs, indicate some degree of blood concentration due to the excessive loss of water by way of sweat glands. However, the latter experiment would appear to show that fever *per se* is not the essential factor in causing convulsions in the subject with latent tetany, when he is subjected to an acute infection or to typhoid vaccine administration.

In order to determine the comparative importance of the parathyroid hormone with its specific influence on calcium and phosphorus economy and the effect of forced water retention, the first experiment above was repeated while parathyroid extract was being administered in comparatively large doses at regular intervals. The essential results are shown in the last section of figure 2. Although the serum calcium rose steadily from a low point of 6.2 mg. per 100 cc. before parathyroid extract was administered to a maximum of 16.6 on the fifth day with fairly active accompanying diuresis, pitressin completely abolished the latter effect and produced a more marked retention of water than that recorded for the previous antidiuresis test. In spite of water retention, sufficient to cause a weight gain equivalent to 5.3 per cent of the initial body weight, the patient did not develop signs of

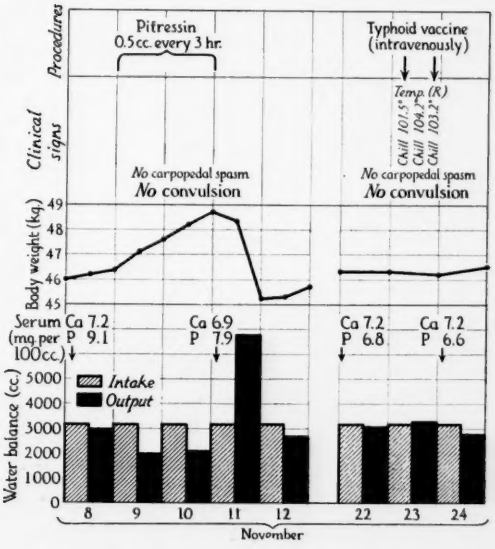

Fig. 3. Effect of adequate mineral diet on convulsive reactivity, as determined by response to pitressin test and to typhoid vaccine administration.

tetany and did not have a convulsion. In this respect his response to the sustained antidiuresis test was like that of the normal subject, whereas without parathormone administration it resembled that of the genuine epileptic patient (10).

Influence of adequate mineral intake. After the patient had been maintained for several months on a diet calculated to contain all of the principal minerals in amounts considered to be adequate for normal maintenance and growth, the pitressin and the typhoid vaccine experiments were repeated.

Data from two such experiments are presented in figure 3. It will be seen that values for the calcium and inorganic phosphorus of the serum were of approximately the same magnitude during this period as they were during the period of low mineral intake.

Nor were they significantly altered by the experimental procedures carried out.

The results of an experiment on the effect of forced water retention (pitressin test) are shown in the first section of the chart. In spite of the fact that the amount of water retained on this occasion as a result of antidiuresis was greater by nearly one liter than that retained during the first experiment (fig. 2), a convulsion did not occur and there were no signs of active tetany.

Ten days following the completion of this experiment, typhoid vaccine was administered intravenously in the same dosages and at approximately the same intervals as in experiment 2 (fig. 2). Although the increase in rectal temperature was greater on this occasion than at the time of the first experiment, no signs or symptoms of tetany and no convulsions were induced. While the slight degree of water retention and the very small decrease in serum calcium noted in connection with the previous experiment were not observed in the present instance, it would not be justifiable to assume that these small differences were sufficient to explain the occurrence of symptoms in the one instance and not in the other. It is worthy of note at this point, that there were no significant differences between the general serum electrolyte patterns for the two dietary periods.

In checking the various differences between the two general dietary regimens, other than the calcium and phosphorus content, which might conceivably contribute to the striking differences in response of the patient, it was observed that the calculated preponderance of alkali over acid in the ash of the 'low mineral' diet was slightly greater than that in the diet with the greater total mineral content. In order to determine the true significance of this particular difference, the foregoing experiments were both repeated after the patient, still on the higher mineral diet, had taken 6 grams of sodium bicarbonate daily for several weeks. That amount of alkali was calculated to make the two diets more nearly alike from the viewpoint of the acid-base balance of the ash.

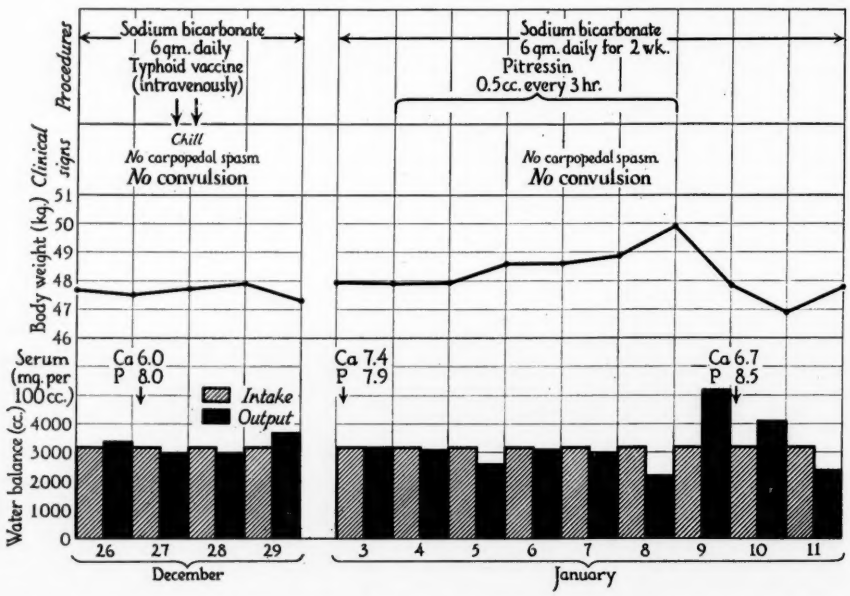

Fig. 4. Effect on convulsive reactivity of additional sodium bicarbonate in adequate mineral diet.

The results of these two experiments are graphically recorded in figure 4. As shown in the first section of the chart, the intravenous administration of typhoid vaccine produced chills and fever as previously and appears to have produced a slight increase in body water as in experiment 2 (chart 2), but did not cause a convulsion or recurrence of the signs or symptoms of tetany. It might be argued that the process of immunity, developing as a result of the original injections, may have modified the patient's response. If this possibility may be judged by the patient's febrile reaction any immunity which may have developed was probably not significant in relationship to the convulsive mechanism, because in this respect the reaction differed but little from that in each of the preceding typhoid vaccine experiments. It should be noted that the serum calcium level was lower by 1.4 mg. per 100 cc. at the beginning of this experiment

than at the beginning of the corresponding experiment during the low-mineral period (exp. 2., fig. 2) and 0.6 mg. lower than the lowest value recorded for that experiment. Unfortunately no determinations of serum calcium and phosphorus were made at the height of the fever in this instance.

In the second section of figure 4 are seen the results of the pitressin test repeated while the patient was still taking the higher mineral diet supplemented by 6 gm. of sodium bicarbonate daily. Although the antidiuresis was sustained for 5 days, as contrasted with 2 days in experiment 1 (fig. 2), and the amount of water retained was approximately the same, no convulsions and no signs of active tetany were observed. The level of the serum calcium was altered but little.

The results of these two experiments indicate that the slightly greater alkaline value possessed by the low mineral diet does not account for the difference in the patient's response to the various experimental procedures used.

After a period of 3 weeks on the low-mineral diet, the patient again showed early signs of tetany but had no recurrence of spontaneous convulsions. It was found at this time that his serum calcium ranged on a somewhat lower level and the inorganic phosphorus on a slightly higher level than those observed at the time of the first experiment. This difference may have been due in part at least to the fact that the earlier observations were made during the months of July and August, while these experiments were carried out in January and February.

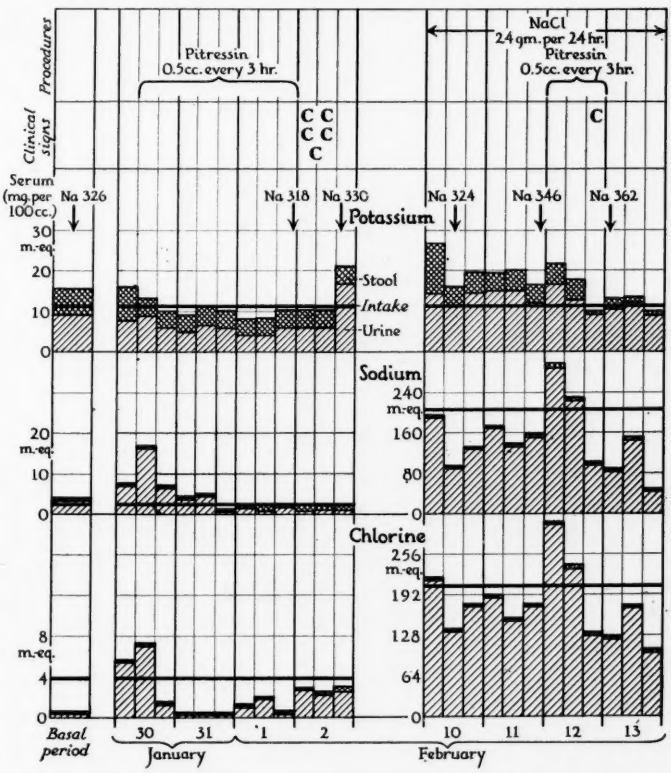

Fig. 5. Effect of sodium chloride administration on response to pitressin test and on K, Na and Cl balances during period of low mineral intake. C = convulsion. Note values for serum Na.

Samples of data concerning the mineral balances for this second period on the low-mineral dietary are shown in the first short sections of figures 5 and 6 under the caption, "basal period." Comparison of these with the values recorded for the first general period (fig. 1) show them to be very similar. The magnitudes of the negative balances for most of the elements are almost identical.

Effects of sodium chloride ingestion on response to pitressin test during period on low-mineral diet. Since it has been shown that the convulsive seizures induced in the genuine epileptic by sustained post-

pituitary antidiuresis can be prevented by ingestion of sufficient sodium chloride to prevent dilution of the extracellular body fluids (10), it was thought desirable to determine the effects of his taking extra quantities of this salt in conjunction with the test. Results of such an experiment, together with those from a control test involving the use of pitressin alone, are presented in figures 5 and 6.

As may be seen from figure 6, the negative balance of the phosphorus and calcium, which characterized the basal period, was abolished during the period of antidiuresis. This was particularly notable in the case of phosphorus. The magnesium excretion by way of the kidneys appears to have been increased. The amount of urinary calcium was so small throughout the period of the low-mineral diet that its variations

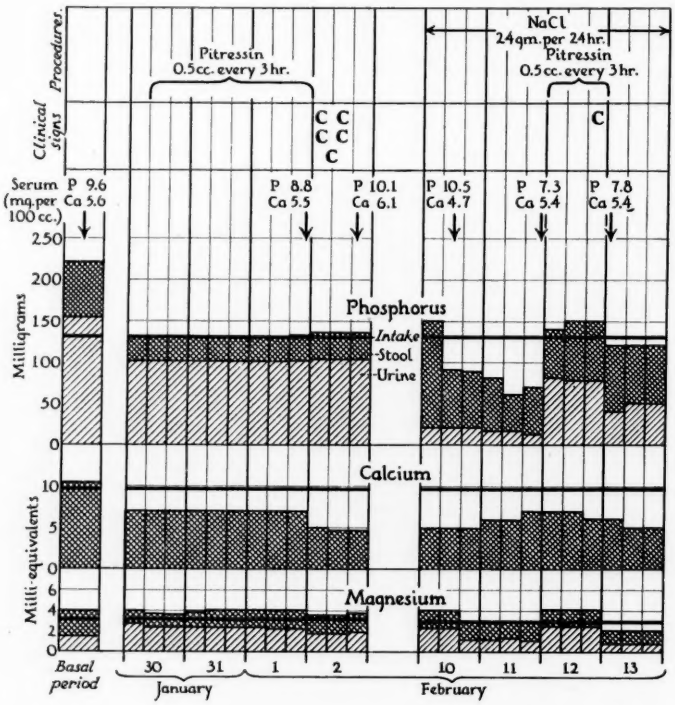

Fig. 6. SAME AS FIGURE 5 but showing P, Ca and Mg balances. Note values for serum Ca and inorganic P.

The results of the control experiment on the effects of sustained antidiuresis are shown in the first section of both figures. It will be seen that five generalized convulsions occurred in rapid succession at the height of the antidiuretic response. Comparison of values for the calcium, sodium and inorganic phosphorus of the serum at the beginning of the test with those obtained just before and again some hours after the occurrence of convulsions reveals no evidence of significant change. No alterations in the levels of the magnesium, potassium or total protein of the serum were observed that would contribute to an explanation of the convulsions. While the hydrogen ion concentration of the blood was not determined in connection with these experiments, this factor has been found on other occasions to remain essentially unaffected by prolonged pitressin antidiuresis.

were insignificant. An attempt to explain the decrease in fecal calcium and phosphorus on the basis of retention in the intestinal tract was not supported by any evidence of a precipitous loss of these elements by this route immediately following the experimental period. The slight increase in serum calcium and inorganic phosphorus found near the end of the postpitressin period of diuresis might be explained as easily on the basis of extracellular fluid concentration from the continued retention of these elements after diuresis as on the basis of increased intestinal absorption after disappearance of the pitressin action. These findings regarding calcium, magnesium and phosphorus, while somewhat suggestive, appear to us to be of doubtful significance as regards the convulsive mechanism.

Eight days following the completion of the foregoing experiment extra sodium chloride was given in

conjunction with the pitressin test. It was administered with the regular meals in doses of 6 gm. every 6 hours for 2 days preceding the test as well as during it. The essential results of the entire experiment are shown in the second sections of figures 5 and 6. It can be seen that the patient had but one convulsion instead of five, as in the control test. The symptoms of neuromuscular irritability were definitely less marked, also. Although the serum calcium was slightly lower and the sodium was significantly higher during the preliminary period of salt ingestion than at any time during the control experiment, the patient did not have a convulsion until he had been given pitressin at frequent intervals for one additional day. According to changes in body weight, the total amount of water retained as a result of the extra sodium chloride taken was greater by 200 gm. than that due to pitressin antidiuresis in the control experiment. Pitressin administration caused retention of an additional 700 gm. of water before the convulsion occurred. The serum calcium and inorganic phosphorus showed no significant changes as a result of pitressin administration.

As would be expected under the conditions, exchanges of sodium and chloride were maintained at a comparatively high level during the entire period with a slightly positive balance throughout, except for the first 12 hours of the day when pitressin was administered. This short period showed a negative balance, as would be expected (11). There was a significant negative balance of potassium, particularly during the first 3 days (fig. 5).

As shown in figure 6, phosphorus and calcium appear to have been retained along with water and sodium chloride as a result of the salt ingestion. Instead of this retention of phosphorus being increased with the increased retention of water during the day of pitressin administration, it was decreased, showing on this occasion a tendency to follow excretion of sodium and chloride. Whereas magnesium showed a tendency to increased retention during the preliminary period of sodium chloride ingestion, it again showed increased excretion as a result of pitressin administration. In this experiment, as in previous ones, the magnesium exchange is seen to vary independently from that of calcium and phosphorus. That these three elements may be metabolized independently, and not necessarily as a group, has been reported previously by Tibbets and Aub (12). Because of the comparatively small amounts of magnesium involved in the mineral exchange under the conditions of the present experiment, it is extremely difficult to appraise its true significance in relationship to the convulsive mechanism. However, this observation is in accord with that of Cooke (13), who found an increased excretion of magnesium in active tetany in animals.

DISCUSSION

From the foregoing results it is apparent that the convulsive reactivity in hypoparathyroidism is not dependent upon the factor of hypocalcemia alone. However, the differences in the patient's response to the various experimental procedures used were obviously related to variations in the mineral and water exchanges. Since the values for the important serum electrolytes showed no significant variations attributable to the dissimilarity in diet during the first two experimental periods, one is practically forced to the conclusion that the observed difference in convulsive tendency was due to different effects of the diets on the tissues of the brain. Eppright and Smith (14) demonstrated that prolonged use of a low-mineral diet, similar to the low-mineral diet of the present study, causes an increase in the water content of various organs. While data for brain tissue were not presented in their report, it is highly probable that the brain responds like other organs to this type of dietary deficiency. Calcium salts were found by these workers to have a protective, dehydrating effect. It has been reported by Baar (9) that the water content of the brain is significantly increased in infantile tetany. Ellis (8) found a similar increase in brain tissue water in experimental parathyreoprivic tetany.

In addition to causing an increase in serum calcium, administration of parathyroid extract induces diuresis, which may be assumed to remove excess water from the tissues. Other procedures or conditions, such as induction of sweating or use of a diet of comparatively high mineral content, which likewise cause removal of excess water, appear to render the sufferer from tetany less susceptible to convulsions, even without a measurable increase in the serum calcium. Within recent years it has been demonstrated by means of the electroencephalograph that a generalized convulsion is the outward manifestation of a disturbance in the electrical activity of the brain cortex (15). It is highly probable, therefore, that the essential factor in the increase in convulsive reactivity in active tetany is not the excess water in the tissues but an associated disturbance in the surface functions of the brain cell membranes, which permits the building up of abnormal electrical potentials. Further experimental studies involving the use of 'tagged' or radioactive isotopes of potassium, sodium, and phosphorus may shed additional light on this aspect of the problem.

SUMMARY AND CONCLUSIONS

1. The convulsive reactivity of a patient suffering from idiopathic hypoparathyroidism was investigated under a variety of experimental conditions.

2. Prolonged use of a diet with a low mineral content was found to increase the convulsive tendency,

as indicated by the patient's response to different provocative measures.

3. A diet with a relatively high mineral content, particularly as regards calcium and phosphorus, was found to decrease the convulsive reactivity, even when the serum calcium and inorganic phosphorus showed no significant increases over values found during the low-mineral diet periods.

4. During periods of low mineral intake typical convulsions could be induced at will by sustained, post-pituitary antidiuresis and by the intravenous administration of typhoid vaccine without significant changes in the serum calcium and inorganic phosphorus.

5. During periods of high mineral intake, on the other hand, convulsions could not be induced by these procedures, even when the levels of serum calcium and inorganic phosphorus were essentially the same as those for the low-mineral periods.

6. Signs and symptoms of active tetany, and even convulsions, could be produced by short periods of voluntary hyperventilation of the lungs during the period of low but not during the period of adequate mineral intake.

7. Administration of parathyroid extract for several days preceding and during a prolonged period of pitressin antidiuresis prevented induction of convulsions by these procedures, even when the mineral content of the diet was low.

8. Artificial fever produced by diathermy during a period of low mineral intake did not provoke convulsive seizures or signs of active tetany, but resulted in an excessive loss of body water by way of the skin. Fever *per se*, therefore, cannot be regarded as the factor responsible for the increase in convulsive tendency which follows the development of acute infections in the tetanic subject.

9. Adding a sufficient amount of sodium bicarbonate to the diet of higher mineral content to give its ash the same preponderance of alkali over acid as that calculated for the lower mineral diet did not lower its protective value measurably.

10. The increase in convulsive reactivity resulting from pitressin antidiuresis during periods of low mineral intake was found to be much less marked, when sufficient sodium chloride was given to prevent or greatly lessen the degree of dilution of the extracellular body fluids caused by the extra water retention.

11. It is concluded that other factors, in addition to a diminished concentration of calcium ions in the extracellular body fluids are involved in the causation of convulsions in hypoparathyroidism. The possible nature of such factors is discussed.

REFERENCES

1. Collip, J. B.: *Medicine* 5: 1. 1926.
2. McLean, F. C., B. O. Barnes and A. B. Hastings: *Am. J. Physiol.* 113: 141. 1935.
3. Luckhardt, A. B., and B. Goldberg: *J.A.M.A.* 80: 79. 1923.
4. Dragstedt, L. R.: *Physiol. Rev.* 7: 499. 1927.
5. Mathien, F.: *Arch. Internat. Physiol.* 44: 516. 1937.
6. Gerstenberger, H. J.: *Am. J. Dis. Child.* 26: 380. 1923.
7. McQuarrie, I., W. H. Thompson and M. R. Ziegler: *J. Pediat.* 8: 277. 1936.
8. Ellis, M. M.: *Biochem. J.* 22: 937. 1928.
9. Baar, H.: *Ztschr. Kinderheilk.* 46: 502, 1928.
10. McQuarrie, I., and D. B. Peeler: *J. Clin. Investigation* 10: 915. 1931.
11. McQuarrie, I., W. H. Thompson and J. A. Anderson: *J. Nutrition*, 11: 77. 1936.
12. Tibbets, D. M., and J. C. Aub: *J. Clin. Invest.* 16: 491. 1937.
13. Cooke, J. V.: *J. Exper. Med.* 12: 45. 1909.
14. Eppright, E. S., and A. H. Smith: *Am. J. Physiol.* 121: 379. 1938.
15. Gibbs, F. A., and E. L. Gibbs: Atlas of Electroencephalography, Lew A. Cummings Co., Cambridge, Mass. 1941.

Sterol Balance in Hypothyroidism[1]

[Sterols and Thyroid]

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THE EXISTENCE of a relationship between thyroid function and serum cholesterol level is well established. The writers have reported that the concentration of serum cholesterol of children with hypothyroidism before treatment varied from 145 to 660 mg. per cent, whereas in normal children it varied from 96 to 308 mg. per cent (1). The onset of thyroid treatment was followed by a marked drop in serum cholesterol of hypothyroid patients. With a daily dose of two grains (128 mg.) of desiccated thyroid the serum cholesterol of patients with hypothyroidism decreased in amounts varying from 117 to 385 mg. per cent (2). When thyroid medication was discontinued the serum cholesterol of patients with hypothyroidism increased greatly in the course of 4 to 20 weeks, reaching levels 98 to 411 mg. per cent above those of the period of treatment in 15 of 17 cases. In normal children the withdrawal of thyroid medication caused an increase of only 10 to 55 mg. per cent (3).

No attempt has been made to our knowledge to investigate the mechanism of hypercholesterolemia of hypothyroidism. That changes in the blood cholesterol level are not directly related to the metabolic rate has been shown by the fact that dinitrophenol raises the B.M.R. without causing a decrease in serum cholesterol (4, 5). Furthermore, it has been shown in experiments on the rabbit that there is a regular and gradual decrease of the B.M.R. after thyroidectomy, whereas there are wide fluctuations of serum cholesterol (6).

This paper is a report on sterol-balance experiments on two patients with hypothyroidism and one sexually immature dwarf who had no evidences of thyroid deficiency. These were made for the purpose of shedding some light on the mechanism of the relationship of thyroid function to serum cholesterol. No experiments of this kind have been reported in cases of thyroid disturbances, although the hypercholesterolemia associated with xanthomatosis has been studied in sterol balance experiments by Schoenheimer (7) and by Thannhauser (8). Schoenheimer (9) discovered that plant sterols are not absorbed and that a patient receiving a vegetable diet does not absorb any sterols with his food. It was, therefore, possible to eliminate cholesterol intake in a metabolism experiment by giving a vegetable diet. He found that the serum cholesterol decreased from 850 to 300 mg. per cent in 50 days when a patient with hypercholesterolemia associated with essential xanthomatosis was given a diet free from animal sterols. On a normal mixed diet the cholesterol rose again and could be brought back to normal by a cholesterol-free diet (7). In another patient with essential xanthomatosis there was a decrease in the serum cholesterol from 657 to 152 mg. per cent (8).

Both in Schoenheimer's (7) and in Thannhauser's (8) case there was practically no excretion of cholesterol or its derivatives in the stools. Since cholesterol was not eliminated it was assumed that in these patients there was probably a slow process of degradation of cholesterol and that there was also a disturbance in the cholesterol-excreting mechanism (7). In the normal person the cholesterol level of the serum is maintained on a cholesterol-free diet (10). The processes of cholesterol synthesis, destruction and excretion are held in balance.

It is to be noted, however, that not all patients having hypercholesterolemia due to xanthomatosis react in the same way and that some have been reported in which a cholesterol-free diet has had no

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effect on the high serum cholesterol level in essential xanthomatosis (8, 11).

METHOD OF STUDY

The plan of our experiment followed the principles of the studies on xanthomatosis mentioned above. The patients were given a diet of fixed sterol content which was very low in animal sterol, containing no meat or fish and only vegetable oils. The only foodstuffs of animal origin used were white of egg (contains no cholesterol), 200 to 300 cc. of skimmed milk (containing 1 mg. of cholesterol per 100 cc. as estimated by the colorimetric method, 12) and the small amount of animal fat used in baking bread. The diets of the three patients studied, calculated according to the food tables of Bridges (13), are listed in table 1.

TABLE 1. DIET OF PATIENTS USED IN STUDY OF STEROL METABOLISM

Patient	Calories	Proteins gm.	Plant sterols mg.	Cholesterol not exceeding mg.
G.S.	1600	35	118	4
D.S.	2200	52	172	6
M.H.	1250	27	96	4

The stools were collected in 6-day periods, marked at the beginning and end by the administration of charcoal. They were dried, pulverized and analyzed for sterol by the digitonin method (14).

Serum cholesterol was determined by the colorimetric method of Bloor, adopted by Pijoan to the Evelyn photoelectric colorimeter (12).

Basal metabolism determinations were made satisfactorily on patients *G.S.* and *M.H.* but patient *D.S.* was not cooperative. The deviations were calculated from the Boothby-Sandiford standards.

The results of the experiments are shown in figures 1, 2 and 3 and are summarized in table 2.

Patient G.S. (*H.L.H. 34878*) is a 25-year-old cretin who was untreated until she came under our observation at the age of 24 years, one year prior to this experiment. At that time her height was 50 inches (height age, 8½ years), her bone age was 12 to 13 years, her B.M.R. was −28%, her serum cholesterol was 418 mg. %. She showed typical cretinoid features. The therapeutic response to thyroid extract was excellent. There was a rapid acceleration of growth, the cretinoid characteristics of her features disappeared, her skin became soft and moist. The B.M.R. was +2% and the cholesterol 135 mg. % one month after the onset of thyroid treatment. Four weeks before admission for the sterol experiment treatment was discontinued so that the patient was decidedly hypothyroid at the onset of the experiment.

From the chart in figure 1 it can be seen that the serum cholesterol was high (319 mg. %) at the onset of the experiment, as was to be expected in a cretin in whom treatment with thyroid had been discontinued. The drop in serum cholesterol at the onset of treatment from 304 to 136 mg. per cent in 16 days, and the rise after discontinuing treatment from 176 to 295 mg. per cent in 18 days are very marked, as are the rise of the B.M.R. from −6 to +37 per cent and the subsequent drop from +32 to +2 per cent. The dotted line marks the average daily intake of sterols (0.12 gm.) of which at least 96 per cent are plant sterols. The average daily output of sterols in the stools is marked by the solid line.

Patient D.S. (*H.L.H. 47498*) is a 17-year-old cretin who was first treated with thyroid at 2½ years of age. The therapeutic response was excellent as regards physical development. Between the ages of 13 and 17 years the influence of thyroid treatment on the serum cholesterol was studied repeatedly and was shown to be of the type characteristic for the cretin, i.e., a sharp rise after discontinuation of treatment and great sensitivity to treatment. The patient received treatment with thyroid, 2 grains daily for 8 months prior to the balance study. During this time the serum cholesterol was fairly constant, between 103 and 117 mg. %.

TABLE 2. DATA ON STEROL METABOLISM IN 2 CRETINS AND 1 NON-HYPOTHYROID DWARF TREATED WITH THYROID

Patient	Before Treatment			On Thyroid Treatment			After Thyroid Treatment		
	Serum cholesterol		Daily average stool sterols	Serum cholesterol		Daily average stool sterols	Serum cholesterol		Daily average stool sterols
	first	last		first	last		first	last	
	mg. %	mg. %	gm.	mg. %	mg. %	gm.	mg. %	mg. %	gm.
G.S., Cretin	319[1]	302	0.26	304	145	0.24	176	280	0.22
D.S., Cretin				121[2]	112	0.24	103	232	0.23
M.H., Control	172[1]	199	0.24	164	133	0.16	126	205	0.16

[1] Off treatment at beginning of experiment.
[2] On treatment at beginning of experiment.

From the chart in figure 2 it can be seen that when her diet was changed to the low-cholesterol vegetable diet there was no significant change in the serum cholesterol which fluctuated between 103 and 135 mg. per cent. After withdrawal of treatment the concentration of serum cholesterol rose sharply to a level of 224 mg. per cent, an increase of 121 mg. per cent in 18 days and then fluctuated between 184 and 242 mg. per cent. The dotted line marks the daily sterol intake of about 0.18 gm., of which the animal sterols were not over 3 per cent. The average daily sterol output in the stools is marked by a solid line, indicating a slightly negative sterol balance throughout the experiment.

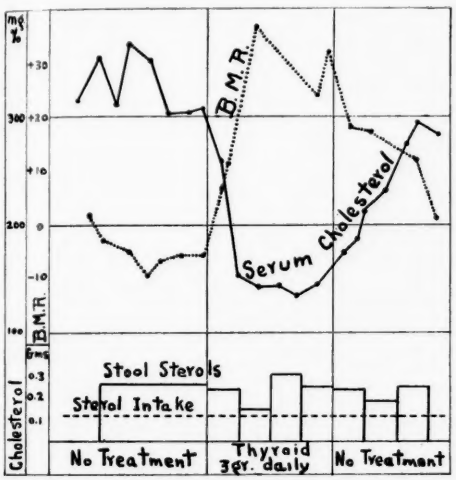

Fig. 1. B.M.R. AND STEROL STUDIES IN A CRETIN. *Patient G. S.*

Patient M.H. (see fig. 3). The control case is *M.H.* (*H.L.H.* 39480), a 17-year-old, mentally deficient, dwarf (height age, 8½ years) with marked sexual infantilism. Thyroid insufficiency was ruled out as the cause of her dwarfism during a previous study on the metabolism ward. Her condition is suggestive of pituitary dwarfism. She had received no thyroid treatment for 6 months prior to her admission. Her serum cholesterol showed fluctuations from 126 to 199 mg. % before treatment (fig. 3). The drop in serum cholesterol from 164 to 118 mg. % after onset of treatment and a rise from 133 to 200 mg. % after withdrawal of treatment are of the order of magnitude which would be expected in a patient not suffering from hypothyroidism. The dotted line shows the sterol intake with the food, which is approximately 0.1 gm. of which not more than 4% are animal sterols. The solid line indicates the average daily sterol output in the stools.

DISCUSSION

In patients with hypothyroidism, as in normal individuals, the concentration of cholesterol in the serum is not affected by a lack of cholesterol in the diet. The high cholesterol level of 319 mg. per cent shown by *G.S.* before treatment did not decrease when cholesterol was eliminated from her diet. In

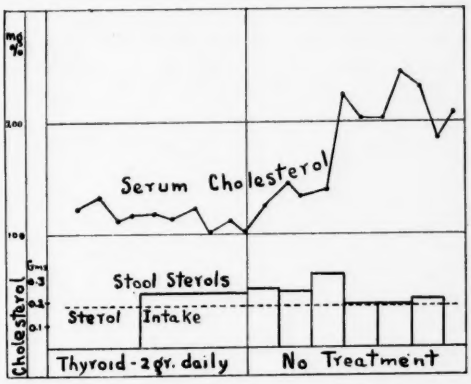

Fig. 2. STEROL STUDIES IN A CRETIN. *Patient D. S.*

the case of both *G.S.* and *D.S.*, although practically no cholesterol was ingested, a typical increase in the serum cholesterol occurred after discontinuing treatment just as occurs in hypothyroid patients receiving a normal diet. In *D.S.* the rise of the serum cholesterol level after discontinuing thyroid treatment which

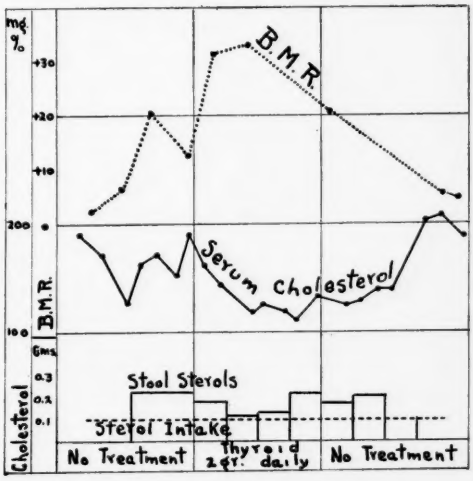

Fig. 3. B.M.R. AND STEROL STUDIES IN A NON-HYPOTHYROID DWARF. *Patient M. H.*

occurred during the experiment on the cholesterol-free diet can be compared with that observed by us during a previous period when she ingested a normal diet. On the low cholesterol diet her serum cholesterol

reached a level of 242 mg. per cent in 29 days; in 1939 on a normal diet her cholesterol rose to 210 mg. per cent in 36 days. There is no indication that the changes in serum cholesterol are influenced by the low cholesterol diet.

That the hypercholesterolemia of hypothyroidism is not due to retention of cholesterol in the body is shown by the fact that there is no marked decrease in the stool sterols during the periods of rising serum cholesterol after discontinuing treatment. In all three patients the sterol balance was negative throughout the experiment.

Even if we assume that the 6 mg. of cholesterol ingested daily with the food were retained and entirely used for a rise in the sterol content of the blood plasma and that none of it were deposited elsewhere in the body, this would only account for a total increase in the body sterols of 180 mg. in 30 days, or a rise in the serum cholesterol of 7 mg. per cent, if the blood volume is assumed to be 4,500 cc. Actually an absorption of 3500 mg. of cholesterol in 30 days or of 117 mg. daily would be necessary to account for the increase in serum cholesterol observed. In *G.S.* the whole of the animal sterols absorbed if taken up entirely by the plasma could only account for a rise of serum cholesterol of 6 mg. per cent under our experimental conditions. To account for the actual rise of 150 mg. per cent observed after discontinuing treatment, the retention in the serum of 2,250 mg. of cholesterol would be necessary, assuming a blood volume of 3,000 cc.

The decrease in serum cholesterol after the beginning of treatment is not due to excretion through the intestine or bile since the analysis showed a fairly constant excretion of stool sterols during the whole experiment and no increase during thyroid treatment. A decrease of serum cholesterol of 150 mg. per cent in patient *G.S.* signifies the disappearance of more than 3,000 mg. of cholesterol from the plasma. If this had been excreted during the first six days of thyroid treatment, we should have had to find about three times more sterol in the stools than we actually did. The sterols of the stools consist of plant and animal sterols. Since it has been shown that the plant sterols are not absorbed, it can be assumed that the amount of plant sterols in the feces is that indicated by the intake in the charts. The rest of the sterols excreted (indicated on the charts as the space between the dotted and the solid lines) is probably composed of cholesterol and its derivatives (coprosterol and dihydrosterol) excreted through the bile and the intestines. We know from the experiments of Schoenheimer and Breusch (14) on mice that "in the tissues cholesterol is continually being formed and destroyed. Either a positive or a negative balance may be found depending upon experimental conditions, i.e. synthesis may be in excess of destruction or vice versa." In their experiments in which mice were fed on a low cholesterol diet the sterol balance was negative, the same as in our experiments.

To exclude the possibility of loss of cholesterol through the urine we examined ether extracts of the urine of patient *G.S.* during her first period of treatment on her previous admission to the hospital, during which her serum cholesterol fell from 522 to 207 mg. per cent and failed to find any traces of sterols. This is in accordance with the known fact that the urine produced by a normal kidney does not contain more than traces of cholesterol (15).

The factors determining the total cholesterol content of the entire body are absorption from the food, excretion, synthesis and destruction (or the transformation of cholesterol into other substances). In our experiment it is shown that the thyroid does not influence the concentration of serum cholesterol through absorption or excretion. If we assume that the serum cholesterol level is an indication of the total cholesterol content of the body, we would have to postulate a great increase of cholesterol destruction at the onset of treatment and an increase of cholesterol synthesis on withdrawal of treatment. No evidence has been offered for this. There is a further possibility that a change in the concentration of serum cholesterol might be caused by alterations in the distribution of cholesterol between plasma and tissues rather than a change in the total cholesterol content of the body. Which of these explanations holds true can be settled only by animal experiments in which one can determine the total cholesterol content of the body and its distribution in various tissues. Such experiments are being carried out.

SUMMARY

Sterol balance experiments are reported on two patients with hypothyroidism and one patient with dwarfism not associated with thyroid deficiency. The patients were given a vegetable diet, which was practically free of cholesterol. The characteristic changes in the concentration of serum cholesterol which ocur on the institution or the withdrawal of thyroid therapy were not affected by the lack of cholesterol in the diet. The studies showed that the fall of the serum cholesterol occurring when thyroid is administered is not due to an increased excretion through the intestine and that the rise of serum cholesterol following the withdrawal of therapy is not due to an increased absorption or retention of sterols. Other explanations for the influence of the thyroid on the serum cholesterol are suggested.

REFERENCES

1. Wilkins, L., W. Fleischmann and W. Block: *Journal of Clinical Endocrinology* 1: 3. 1941.
2. Wilkins, L., W. Fleischmann and W. Block: *Journal Clinical Endocrinology* 1: 14, 1941.
3. Wilkins, L., and W. Fleischmann: *Journal Clinical Endocrinology* 1: 91. 1941.
4. Cutting, W. C., D. A. Rytand and M. L. Tainter: *J. Clin. Invest.* 13: 547. 1934.
5. Grant, F. L., and P. G. Schube: *J. Lab. and Clin. Med.* 20: 56. 1934.
6. Fleischmann, W., H. B. Shumacker, Jr. and L. Wilkins: *Am. J. Physiol.* 131: 317. 1940.
7. Schoenheimer, R.: *Ztschr. klin. Med.* 123: 749. 1933.
8. Thannhauser, S. I.: Lipidoses: Diseases of the Cellular Lipid Metabolism. Oxford Medicine 4: 214. 1940.
9. Schoenheimer, R.: *Science* 74: 579. 1931.
10. Barreda, P.: *Klin. Wchnschsr.* 13: 290. 1934.
11. Sperry, W. M., and B. Schick: *Am. J. Dis. Child.* 51: 1372. 1936.
12. Pijoan, M., and C. W. Walter: *J. Lab. and Clin. Med.* 22: 968. 1937.
13. Bridges, M. A.: Food and Beverage Analyses, Lea and Febiger, Philadelphia, 1935.
14. Schoenheimer, R., and F. Breusch: *J. Biol. Chem.* 103: 439. 1933.
15. Gardner, J. A., and H. Gainsborough: *Biochem. J.* 19: 667. 1925.

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Clinical Applications of Studies in Experimentally Induced Exophthalmos of Anterior Pituitary Origin

[Exophthalmos]

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ALTHOUGH THE PATHOGENESIS of exophthalmos in exophthalmic goiter has been the subject of considerable speculation, it has been possible to bring relatively little direct experimental investigation to bear on the problem. This situation has arisen because opportunities for such experimental studies on man are obviously limited. Investigations of this condition have been further hampered by the fact that, until quite recently, exophthalmos could not be produced at will in lower mammals. Now that this is possible, a further obstacle to progress lies in the fact that results obtained in one species are not freely applicable to that of another species. Various species differ in their physiological responses to what appears to be an identical stimulus. These variations in response may be due to constitutional characteristics inherent in individuals belonging to different species, but, as in the case of the orbital cavity, the anatomical structure as such may determine the type of response which a stimulus elicits. The anatomy of the human orbit differs significantly from that of lower mammals, a fact which must be taken into consideration in the interpretation of the experimental evidence.

Anatomy of the Orbit in Man and Mammals and Effect of Cervical Sympathetic Stimulation upon the Position of the Eyeball in Mammals

The musculus orbitalis of Müller, which is found only in a vestigial form in the inferior orbital fissure of man (1), is an important well developed muscle in lower mammals (2). In the latter it is composed chiefly of layers of elastic tissue and smooth muscle fibers (membrana orbitalis musculosa) which complete the lateral wall of the orbit where the bone is absent and serve as an elastic muscular tunic for the eyeball. Müller reported that stimulation of the cervical sympathetic nerves caused contraction of the muscle and protrusion of the eyeball of mammals in which the muscle acted upon the eyeball. He also reported that in some instances the musculus orbitalis was antagonized by a special 'retractor bulbi' muscle. Coincidentally and independently, Claude Bernard (3) reported similar observations in rabbits after cervical sympathetic stimulation.

Sappey (4) likewise found that stimulation of the upper end of the superior cervical sympathetic ganglion caused protrusion of the globe. He attributed the exophthalmos to contraction of smooth muscle fibers in the orbital aponeurosis which forms a sheath about the eyeball. He found these involuntary fibers distributed over a wide area in the sheath but collected into more distinct bundles at certain points, thus transforming the aponeurosis into a contractile cuff or muff in the form of a cone with a fixed base at the septum orbitale and its apex posteriorly. When the muff contracted, it pressed on the posterior aspect of the globe and squeezed it forward.

Harling (5) made an exhaustive study of the anatomy of the membrana orbitalis in man and lower mammals. He agreed that the muscle was vestigial in man and that it could not play a rôle in the mechanism of exophthalmos. He described two groups of smooth muscle fibers of varying thickness which ran circularly and longitudinally in the elastic tunic surrounding the globe. The circular fibers, which took a course parallel to the margin of the orbit were more strongly developed than the longitudinal bundles, which were present only at a few places at the inferior margin of the orbit. Because of its funnel shape and anterior attachments, he suggested that when stimulated, the muscular sheet became flattened (similar to the diaphragm during contraction) and pressed the eyeball forward by virtue of the fact that it decreased

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the volume of the orbital cavity posterior to the eyeball.

MacCallum and Cornell restudied the problem in 1904 (6). They too identified a cuff of smooth musculature and elastic tissue which formed a conical mantle about the eyeball in man and lower mammals, and likewise concluded that it was far better developed in the dog. The cone of muscle was found to be continuous anteriorly with the musculature of the eyelids, formed abundant attachments about the margin of the orbit, and then passed backward to end around the optic foramen. By removing the top and side of the orbit in a dog they laid bare the bulb from the surrounding fat and could observe that stimulation of the cervical sympathetic nerves resulted in a distinct peristaltic wave which passed backward throughout the length of the cone and pressed the eyeball forward. They then cut around the middle of this cone so that the anterior was completely severed from the posterior portion. Cervical sympathetic stimulation now caused contraction of the posterior or small end of the cone, which retracted out of sight into the optic foramen, while the eyeball remained stationary.

Code and Essex (7), who have more recently reexamined the problem in dogs with MacCallum's technique, confirm most of the previous investigators in essential details. They found the entire orbital contents with exception of the lacrimal gland to be enclosed in a conical fascial sheath. The base of the cone was attached to the orbital margins anteriorly and its apex to the foramina of the orbit posteriorly. The superior surface of the sheath was composed of alternating layers of elastic and connective tissue, directly continuous with which were strands of smooth muscle fibers. Cervical sympathetic stimulation caused circular contraction of the cone-shaped sheath which squeezed the eye forward into the position seen in exophthalmos.

The apparent significance of these findings has been tempered somewhat by the experiments of Essex and Corwin (8). Making use of an exophthalmometer, they found that in the dog the eyeball recedes 2.5 to 5 mm. during anesthesia with sodium amytal, sodium phenobarbital and chloralose. Surgical ether anesthesia, however, induced a mild exophthalmos with the eyeball protruding approximately 1.5 mm. beyond its original position. Cervical sympathetic stimulation in anesthetized dogs or the administration of tyramine or ephedrine to normal and anesthetized animals caused the eyes to advance about 1 mm. beyond their original positions. Their results with sympathomimetic drugs are not surprising, but the absence of more pronounced exophthalmos on stimulation of the cervical sympathetics is unexpected.

Effect of Stimulation of the Cervical Sympathetics upon the Position of the Eyeball in Man

Experiments of this kind in man have naturally been few. Wagner (1860) reported two cases in which the cervical sympathetics were stimulated electrically immediately after decapitation for a capital offense (9). He did not observe exophthalmos, nor did MacCallum and Dandy (1904) who reported a similar attempt in two patients in whom these nerves were stimulated incidentally during the course of operations for other reasons (10). Troell (1916) tells of another such experiment which was likewise unsuccessful (11). Jonnesco (1900), on the other hand, thought he observed several positive responses (12). In none of these experiments was the position of the eyeball determined by accurate measurements. This has been done by Friedgood, Cattell and Beetham (13) who have studied a selected group of 10 cases thus far. Eight of these patients who were without exophthalmos, had primary hyperthyroidism or adenomatous goiter with hyperthyroidism (Lahey's nomenclature). Of the other two patients who did have exophthalmos, one had primary hyperthyroidism, and the other, myxedema. Thyroidectomy was done in the 9 cases of hyperthyroidism; the exophthalmos of the patient with myxedema was treated by bilateral superior cervical sympathetic ganglionectomy. After completion of the thyroidectomy, the right or left cervical sympathetic trunk was anatomically identified and dissected out. A bipolar electrode with platinum tips 5 mm. apart was then brought into contact with its fibers. Electrical excitation of the nerve was induced by condenser-discharge stimuli at the rate of 20 to 25 per second, which is the optimal rate of stimulation of sympathetic fibers (cf. 14 for literature). Measurements of the position of the eyeball relative to a fixed point on the orbital rim were carried out with the Hertel exophthalmometer. By means of a system of mirrors in this instrument one can determine the distance from the plane of the most anterior portion of the cornea to that of a fixed point such as the lateral bony orbital rim. The amount of soft tissue between the instrument and the bony rim and the variation in the amount of pressure applied in holding the instrument in place, makes for a possible error of several millimeters in the readings obtained on the same patient by different observers. If, however, the readings are done by one observer and in a constant fashion, this error can be reduced to as little as 1 mm. in a series of consecutive readings.

As a result of the cervical sympathetic trunk stimulation, which was maintained for 30 to 45 seconds, the pupil always dilated to its widest diameter and there was a definite slight retraction of the upper eyelid, presumably due to stimulation of Müller's muscle. In one instance the pupil remained dilated

for almost two minutes after stimulation was discontinued. A significant change in position of the eyeball was not observed in 9 of the cases. In one instance, however, the eyeball moved forward unmistakably for a distance of 3 to 4 mm. This occurred in the only patient in our series who had well defined exophthalmos associated with the hyperthyroid state.

One patient developed a persistent Horner's syndrome which was attributed to trauma of the sympathetic trunk incident to its dissection. In this case there was excessive lacrimation with epiphora, a moderate degree of ptosis of the lid and persistent contraction of the pupil postoperatively. The excessive lacrimation disappeared within the succeeding 9 months, and the ptosis became barely perceptible; but the pupil remained one millimeter in diameter smaller than that of the unoperated side.

It may be concluded tentatively from these experiments that the position of the eyeball is not ordinarily influenced by electrical stimulation of the cervical sympathetics in patients who have hyperthyroidism without exophthalmos. This is not surprising in view of the fact that dogs, who have an abundance of orbital smooth musculature under the influence of the sympathetics, do not develop a significant amount of exophthalmos in similar circumstances (8). It is interesting that definite protrusion of the globe was noted during stimulation of the cervical sympathetics in the one case in which the eyeballs were already in the exophthalmic position. Further observations will have to be made before one can do more than comment on the significance of these preliminary experiments.

Production of Exophthalmos with Anterior Pituitary Extracts

Although the relation of the cervical sympathetics to the pathogenesis of exophthalmos is still an incompletely solved problem, there can be little question about the exophthalmos-producing property of extracts of the anterior pituitary gland.

In 1923, Hogben reported that the injection of Armour's fat-free desiccated anterior pituitary lobe extract resulted in the metamorphosis of normal and thyroidectomized axolotls (15). Spaul repeated these experiments on normal tadpoles and axolotls with Messrs. Oppenheimer's commercial anterior pituitary extract and likewise observed metamorphosis (16). Both investigators noted that bulging of the eyeballs was one of the early manifestations of such metamorphosis. Schwartzbach and Uhlenhuth (17) demonstrated, however, that the thyroidectomized axolotl could not be metamorphosed with anterior hypophyseal extracts which they had prepared themselves.

On the basis of an extensive series of experiments, Loeb, Bassett and Siebert (18, 19) reported data which obviously supported those of Schwartzbach and Uhlenhuth. They found that Armour's anterior lobe powder contained large amounts of iodine and acted in a manner similar to that of thyroid substance. This disclosure explained satisfactorily the reported discrepancies, because Gudernatsch had already shown that the administration of thyroid resulted in the metamorphosis of thyroidless amphibian larvae. Presumably, Spaul's commercial anterior pituitary extract (Messrs. Oppenheimer) did not contain thyroid extract, but its iodine content is unknown. It has since been shown repeatedly that exophthalmos can be produced in avian and mammalian subjects by injections with extracts of the anterior pituitary gland.

Schockaert was the first to comment specifically on the exophthalmos which results from the injection of anterior pituitary substance (20). The ducks with which he worked developed hyperthyroidism within the first week of the experiment and showed exophthalmos on or about the 20th day of injection. If the injections of extract were stopped, the exophthalmos disappeared within 1 to 2 weeks. The exophthalmos is said to have vanished promptly during ether anesthesia and to have reappeared slowly as the duck awakened. Loeb and Friedman confirmed Schockaert's work using the guinea pig as an experimental animal (21). Their report does not include the total number of animals studied, nor the percentage which developed exophthalmos. They first noted the appearance of exophthalmos after 4 to 6 daily injections of an acid extract of the anterior pituitary gland, and found that it disappeared in complete narcosis, malnutrition and death. The relatively brief duration of their experiments accounts for this observation. The present author noted (22) similar decreases in exophthalmos very early in the experimental period (due no doubt to a decrease in the normal tone of the sympathetic nervous system), but the position of the eyeball was not affected appreciably by narcosis or death once the exophthalmos was well established.

Neither Schockaert nor Loeb and Friedman studied the behavior of the exophthalmos over a prolonged period of time, nor did they correlate the extent of exophthalmos with the state of function of the thyroid gland.

Relation of experimental exophthalmos to the course of hyperthyroidism in guinea pigs injected daily for 6 months with anterior pituitary extracts. An investigation of this problem was made for the first time during 1932–34 (22). It was found that the hyperthyroidism induced by daily injections of an alkaline extract of the anterior hypophysis lasts about 2 to 3 weeks, after which the basal metabolic rate falls to a slightly subnormal level in spite of continued injections of the extract. Exophthalmos appeared in 9 of 30 treated

guinea pigs during the height of the hyperthyroidism, but it became more marked when the hyperthyroidism declined, and was most striking when the basal metabolic rate became abnormally low. It was concluded that a decrease in function of the thyroid favored the development and persistence of exophthalmos which results from daily injections of this extract. As a matter of fact, the entire absence of thyroid function makes the exophthalmos-provoking action of such extracts even more effective because exophthalmos appears more promptly and more frequently in thyroidectomized guinea pigs than in normal ones (23).

It is generally agreed that exophthalmos in exophthalmic goiter is not due to the hyperthyroidism *per se* and that exophthalmos cannot be induced by the administration of thyroid to a normal animal. Moreover, it is commonly recognized that exophthalmos is not necessarily present even in severe cases of exophthalmic goiter. Exophthalmos may frequently appear for the first time after subtotal thyroidectomy for exophthalmic goiter; or, having been present before operation, can become worse afterwards. Ruedemann (24), who has made an extensive study of exophthalmos in postoperative exophthalmic goiter, attributes its development to a deficient thyroid secretion which is characterized in most cases by a progressive lowering of the basal metabolic rate. In a case of this sort he found edema of the upper and lower eyelids and a classical picture of postoperative myxedema. That myxedema can in some circumstances either be responsible for or favor the development of exophthalmos is well known. Gley (25) was the first to report that thyroidectomized rabbits might develop myxedema spontaneously; and Marine and Rosen (26) have found that thyroidectomized rabbits are much more likely to develop cyanide-induced exophthalmos than are unoperated controls. Rabbits are highly sensitive subjects for this experiment, but the condition apparently also occurs with some rarity in the myxedema of man (cf. unpublished data of Friedgood, Cattell and Beetham).

Thomas and Woods (27) studied 15 cases of progressive exophthalmos following thyroidectomy. In those orbits which were explored, they found Tenon's capsule displaced anteriorly by edematous hypertrophied retrobulbar tissue. On the basis of their experience, these investigators conclude that exophthalmos may develop in the absence of clinical hyperthyroidism; but they do not consider that hypothyroidism is an essential predisposing factor. In an effort to justify their belief that thyroid insufficiency is not an important factor in the pathogenesis of post-thyroidectomy exophthalmos, they point out that total ablation of the thyroid in the treatment of cardiac failure does not induce exophthalmos. They overlook the fact, however, that the fundamental pathological physiology prior to operation differs completely in both instances. In the case of the cardiacs, the function of the endocrines is to begin with essentially unaffected; in that of the goiter patients, there already exists a stimulus which is potentially or actually exophthalmos-inducing. It is true that thyroidectomy in exophthalmic goiter generally affects this stimulus favorably by interrupting whatever it is that initiates the entire goiter syndrome; but in the light of other well known evidence it appears likely that in a small percentage of cases a serious form of exophthalmos may be induced by this operation. The protective action of an intact thyroid function against the development of exophthalmos is further substantiated by Soley's experiments (28). He found that there was an increase in prominence of the eyes of a majority of the patients with toxic diffuse or toxic nodular goiter following subtotal ablation of the thyroid, although clinically the eyes appeared less prominent. The apparent improvement of the exophthalmos was due mainly to disappearance of the staring expression which results from retraction of the upper lids. Observations similar to these have in the past been limited to the more striking postoperative complication of malignant exophthalmos. Quantitative methods of observation such as Soley's should give us greater insight into the relation of thyroid function to exophthalmos in Graves' syndrome.

Possible nature of the exophthalmos-producing (ophthalmotropic) substance in anterior pituitary extracts. It is commonly believed without adequate evidence that the thyrotropic factor in an extract of the anterior pituitary can induce exophthalmos as well as thyroid stimulation in guinea pigs. The evidence, as a matter of fact, is quite to the contrary, and was elicited during the course of the experiments already described (22). It is well recognized that in spite of the daily administration of such an extract, the basal metabolic rate returns to a normal level or somewhat below it within a period of 2 to 3 weeks. As one continues the daily injections of such an extract over a period of 6 months, there are recurrent bouts of hyperthyroidism at irregular intervals. It was noted that these recurrent increases in metabolic rate came soon after a fresh batch of the same extract was started, but it was found that the age of the extract was not the determining factor. A clue to the nature of this phenomenon was suggested by an experiment in this series in which the period of hyperthyroidism was prolonged far beyond the usual 2 to 3 weeks by switching from an extract prepared by Schering-Kahlbaum to one manufactured by Squibb before the animal became refractory to the thyrotropic effects of the former. The basal metabolic rate of one of these animals (*12a* ♂) was kept elevated

for more than 84 days (22). The different methods used in the preparation of these two extracts and the fact that the first was more highly purified than the second suggested that the different protein content (and therefore the antigenic potency of the extracts) might have had something to do with the results which were obtained by their alternate use. This belief was strengthened by the knowledge that different batches of the Squibb extract, with which most of the long term experiments were made, also differed in their protein content somewhat (some were more highly purified than others). These details were omitted from the original report inasmuch as they were considered highly theoretical at that time, but an 'anti-pituitary' factor was mentioned as one of the possible explanations for the refractory state. In a subsequent publication the antigen-antibody thesis was more fully developed with the foregoing considerations in mind (29). During a discussion with Dr. P. E. Smith of the possible relation of these experimental findings to the protein content of the extract, he suggested the desirability of studying the same problem with extracts which were deliberately prepared with known differences in protein content. Werner undertook this study in his laboratory and confirmed the earlier observations on refractoriness (30). He also repeated the author's experiment of using alternately two differently prepared extracts of the anterior pituitary and was likewise successful in prolonging the hyperthyroid state beyond its usual duration (31). In extending these observations he found that the period of hyperthyroidism could be maintained for several months provided that the guinea pigs were injected with a flavianic acid extract whose antigenic properties were known to be limited. Werner then concurred in the belief that an antigen-antibody phenomenon was responsible for the refractoriness which animals develop to daily injections of the thyrotropic hormone.

If one accepts this antigen-antibody explanation for the spontaneous decrease in basal metabolic rate during the second or third week of the daily administration of anterior pituitary extract, then one must assume that the antigenic thyrotropic substance has been inactivated by specific antibodies. In these circumstances it is clear that the exophthalmos producing (ophthalmotropic) substance in the extract differs from that of the thyrotropic hormone in its antigenic properties and presumably, therefore, it is a different substance from that which stimulates the thyroid gland. It is doubtful that a difference in the sensitivity of the end organs (in this case the orbital tissues and thyroid gland) could account for persistence of the effect of the thyrotropic substance on the orbital tissues while it completely loses its effect on the thyroid gland. The chances are otherwise, since the thyroid gland of the guinea pig is extremely sensitive to small doses of thyrotropic hormone, while the percentage of animals developing exophthalmos is substantially less than that developing hyperthyroidism.

Since experimental observations indicate that the thyrotropic and ophthalmotropic effects are produced by the same extract, it is quite likely that the substances having these actions are as yet unseparated because they have similar chemical properties. Not only are these substances in close chemical association, but they are also intimately related in their physiological activities. It is characteristic of the pituitary gland that when its function is disturbed in one direction there is frequently a coincidental upset in another. Consequently, differently acting pituitary substances may be secreted coincidentally in increased quantities when the function of this gland becomes abnormal. This circumstance is well illustrated clinically by those cases of hyperthyroidism or diabetes mellitus which date their onset from the menopause. In such cases the increased gonadotropic activity of the anterior pituitary gland which occurs in the menopause is conducive to, or associated with, an increased secretion of the thyrotropic or diabetogenic factors. The latter consequently represent forms of hyperthyroidism and diabetes mellitus of anterior pituitary origin. Thus a variety of pituitary substances with obviously different effects may be elaborated and secreted simultaneously in response to a stimulus which presumably is directed at only one of them. This may account for the coincidental secretion of the thyrotropic hormone and the exophthalmos-provoking (ophthalmotropic) substance in the following circumstances. Hertz, Williams and Means (32) and Rawson (33) have found that a large percentage of patients with so-called malignant exophthalmos show abnormal quantities of thyrotropic hormone in the urine, whereas the urine of normal individuals and of ordinary cases of exophthalmic goiter does not contain any of this substance. The fact that not all patients in this group excrete excessive amounts of thyrotropic hormone suggests that excessive secretion of the latter is a common but not essential part of the syndrome. Another factor must therefore be responsible for the exophthalmos in such circumstances. Another point against the identity of these two factors is that excessive quantities of the thyrotropic hormone are found in the urine of myxedema patients who only rarely develop exophthalmos.

Pathological Physiology of Exophthalmos

As pointed out in the introductory remarks of this paper, it is ordinarily hazardous to compare the experimental findings in one species with those of another. There is now reason to believe, however,

that the exophthalmos in anterior pituitary hyperthyroidism of guinea pigs is sufficiently like that of certain cases of exophthalmic goiter to permit such a comparison.

The pathological physiology of the conditions leading to the development of exophthalmos in exophthalmic goiter is unknown. Essentially two types of exophthalmos are recognized clinically in this syndrome. One is unremitting and rapidly attains serious proportions, the other is that ordinarily encountered in the classic goiter syndrome. The author's studies of experimental anterior hypophyseal exophthalmos in guinea pigs indicate that these two types of proptosis may have a common origin and that the differences in their clinical behavior are due to the presence or absence of factors which modify the ophthalmotropic activity of the pituitary extract.

The first observations to be made of chronic exophthalmos in the experimental guinea pig syndrome (22) disclosed that the proptosis went through a reversible and an irreversible phase. During the early weeks of the daily administration of pituitary extract, this experimental exophthalmos fluctuated in prominence, and disappeared if the injections were discontinued; but if the injections were continued for several months and then discontinued, the exophthalmos persisted unabated. The changes in the orbit were apparently reversible early in this syndrome, but became irreversible eventually. Aird (34), who confirmed and extended these observations, found that the pathological anatomy of the orbital tissues and extraocular muscles in the irreversible phase of the guinea pig's exophthalmos is identical with that which Naffziger (27) and others had described for the orbital contents in patients with postoperative malignant exophthalmos. Smelser (35), who has also confirmed the author's previous observations of chronic pituitary-induced exophthalmos, investigated the retrobulbar tissue changes responsible for the proptosis. His pathologic studies showed that the same retrobulbar tissue changes occurred in the exophthalmos of man and of pituitary-injected thyroidectomized guinea pigs. The exophthalmos was due to increased amounts of orbital tissue (fat, connective tissue and muscles), and there was a great deal of edema of these retrobulbar tissues. Less lymphocytic infiltration and involvement of the extraocular muscles were found in guinea pigs than in man. Paulson (36), who also studied this problem was impressed with the marked edema which he found in the extraocular muscles, retrobulbar fat and loose connective tissue. This evidence, as a whole, links an important aspect of Graves' disease securely to its counterpart in the experimental animal syndrome.

One may assume for the present, until further evidence is brought to bear upon the problem, that ordinary exophthalmos in exophthalmic goiter and so-called malignant exophthalmos represent reversible and irreversible phases, respectively, of this phenomenon. In such circumstances, a single stimulus could be responsible for the development of both types of exophthalmos; the so-called malignant type would occur clinically only when certain conditions favored the onset of the irreversible phase. The intensity of the exophthalmos-producing stimulus must be one of these conditioning factors, and another is apparently a decrease in function of the thyroid gland. There are probably a number of other factors which play an important rôle in this connection. The sex of the individual and the state of function of the gonads are probably among those which significantly influence the exophthalmos-producing stimulus. Hertz, Williams and Means (37) have pointed out that malignant postoperative exophthalmos is much more common in males than in females. Marine (38), who reviewed 52 such cases reported in the literature up to 1936, found that the group consisted of 51 males (60%) and 21 females (40%), respectively. It is an interesting coincidence that Marine's experimental studies of methyl-cyanide exophthalmos in rabbits have yielded a similar correlation between that type of exophthalmos and sex. Cyanide exophthalmos develops most frequently in young, sexually active, male rabbits and is greatly ameliorated or prevented from developing by gonadectomy (38).

Judging from the clinical course of both types of exophthalmos, the changes in the orbital tissues which are responsible for protrusion of the eyeballs must be in part of a labile nature. The prominence of proptosis in acute exophthalmic goiter may fluctuate quite readily from time to time; and exophthalmos often recedes fairly rapidly in a post-thyroidectomy remission. Moreover, the development of malignant postoperative exophthalmos is frequently of strikingly sudden onset and rapid progression. As indicated in the opening paragraphs of this paper, there is no acceptable evidence upon which to postulate that the muscles of the orbit take a significant part in the pathogenesis of exophthalmos. Nor is it conceivable, on the basis of this evidence, that engorgement of the blood vessles *per se* could account for this condition, although this factor has not yet been studied exhaustively. Careful studies of the orbital contents of patients dying with acute exophthalmic goiter show surprisingly little. Friedenwald (39) found the extraocular muscles of 6 such patients entirely normal, and those in a seventh case were slightly enlarged and showed degenerative changes and cellular infiltration. On the other hand, Moore (40), Thomson (41), Burch (42), Naffziger (43), von Zalka (44) and others have described striking pathological changes (vide infra) in the extraocular muscles

of patients with post-thyroidectomy exophthalmos. Thomas and Woods (27) have been impressed with the edema of the other orbital contents in this condition. In one of their cases biopsy of the external rectus showed normal muscle; in other cases they found degenerative and infiltrative lesions. In two of their series the orbital contents were under definite tension when the orbit was explored and orbital fat extruded, although it did not appear increased in amount. In another case, the eye went to enucleation, following which the orbital contents continued to increase in amount and finally bulged out of the orbit. Examination of a specimen of this disclosed edematous but otherwise normal connective tissue and fat. No muscles were identified, but round cell infiltration was found in the redundant conjunctiva.

The evidence from these and other observations indicates that three pathological changes are characteristic of so-called malignant post-thyroidectomy exophthalmos:

a). Marked enlargement of the extraocular muscles with edema, lymphocytic infiltration and fragmentation of muscle fiber.

b). Edema of the orbital fat and connective tissue.

c). Increase in the amount of fat and retrobulbar connective tissue which, with the exception of the edema, appear to be normal histologically.

The encroachment of these space-occupying pathological changes on the contents of the non-distensible orbital cavity adequately accounts for the progressive and serious nature of such proptosis. Available evidence indicates that this is the human counterpart of the irreversible phase of exophthalmos which was observed in the guinea pig syndrome. Analysis of the foregoing pathology discloses that only one of the three changes mentioned could possibly be reversible, viz., the edematous condition of the orbital tissues. Can it be that a disturbance in water balance leading to edema of the orbital tissues is the immediate cause of exophthalmos in acute exophthalmic goiter? This would account for the essentially negative postmortem findings in the orbits of many such patients and fits in with the edema (puffiness) of the eyelids which is not uncommonly seen in exophthalmic goiter. Whether or not the irreversible pathological changes are merely secondary to damage done by edematous infiltration of the retrobulbar tissues is a problem for further study. This is not quite likely since the marked increase in the fat and connective tissue content of the orbit is also in need of explanation.

The effect of the exophthalmos-producing substance, particularly in postoperative malignant cases, is especially noteworthy because of its predilection for the orbital tissues, although patients thus afflicted often show evidence of edema elsewhere (e.g. pitting edema over the tibiae). This is apparently not the only substance which acts thus, since paraphenylenediamin hydrochloride exhibits a similar property and likewise induces exophthalmos, the anatomical cause of which is edema of the orbital tissues (11). This chemical, which thus affects dogs and monkeys, also causes increased epiphora, chemosis and injection of the conjunctivae—findings which closely parallel the eye signs in malignant post-thyroidectomy exophthalmos.

The use of the word *ophthalmotropic* does not imply that a specific chemical substance having this physiological action is believed to exist as such in the pituitary gland. The fact that the ophthalmotropic activity of the extract is probably directly or indirectly responsible for the edema of the orbital tissues suggests that it may be tied in with the important rôle which the pituitary plays in regulating water metabolism. That this may be a generalized disturbance in water metabolism is suggested by two other observations.

a). The edema in patients of this type may be particularly impressive in the orbit, but it has also been observed in other tissues, e.g., over the tibiae.

b). An impaired function of the thyroid gland is apparently a common finding in this type of patient. How this contributes to the tendency to develop exophthalmos is unknown, but it is well to recall that the thyroid influences water metabolism and may have an essential relation with the pituitary gland in maintaining a proper water balance.

Clinical Differentiation of Special Eye Cases from the Ordinary Syndrome of Exophthalmic Goiter

The observations which have been presented indicate that exophthalmic goiter is a syndrome in which either the thyroid or the eyes may become the outstanding problem in therapy. It is essential, therefore, to be able to differentiate clinically between these two types of cases. In the one, thyroidectomy is at present usually the treatment of choice, while, in the other, this operation may precipitate a disastrous ocular complication. Our clinical experience is still too limited to speak with assurance of this differential diagnosis, but where so much is at stake in the choice of therapy, one is justified in being guided for the present by certain common sense clinical criteria and by the experimental laboratory data which have been recorded in detail throughout this paper.

Since edema of the orbital tissues is probably an early pathological change in this type of case, one should regard with suspicion any preoperative chemosis, lacrimination or puffiness and venous conges-

tion of the eyelids. The development of hypothyroidism during iodine therapy or the presence of thyrotropic hormone in the urine should likewise put one on guard, since these findings are associated with an abnormal decrease in thyroid function which is undoubtedly a predisposing factor in the development of ocular complications. As a matter of fact, a decrease in metabolic rate to hypothyroid levels during iodine therapy may be a contraindication to thyroidectomy even if exophthalmos is not the major consideration. Haines (45) and Thompson and his associates (46, 47) have described a group of patients with exophthalmic goiter in whom the administration of iodine causes a significant fall in basal metabolic rate to what are ordinarily considered moderate hypothyroid levels (seldom below −20%). The latter may occur with or without clinical evidence of hypofunction of the thyroid gland (myxedema). The significance of this clinical observation became clear during a study of iodine treated experimental anterior hypophyseal hyperthyroidism in guinea pigs (29, 48, 49, 50), and led the author to postulate that patients reacting in this manner to iodides were entering upon a favorable phase (remission) of their malady and were more suitable for continued treatment with iodides rather than for thyroidectomy (29, cf. chart 3). Hertz and Means (51) subsequently found this to be a valuable guide in their selection of cases for non-surgical treatment. Finally, one should hesitate to operate on individuals, particularly males, who have exophthalmos which is a more striking part of the syndrome than their hyperthyroidism or thyroid enlargement.

The features which have already been mentioned should likewise be warning signals in the postoperative period. An increase in exophthalmos, the development of edema or venous congestion of the eyelids and a relatively low basal metabolic rate, especially if associated with an increasing blood cholesterol or the appearance of thyrotropic hormone in the urine, may be significant premonitory findings.

The medical treatment of postoperative malignant exophthalmos, once it has developed, is notoriously unsatisfactory. Desiccated thyroid, either alone or in combination with iodine, has had only meager success in our hands; and apparently this is also the experience of others. The administration of large doses of estrogenic hormone in an effort to depress the activity of the anterior pituitary gland in a case of menopausal hyperthyroidism met with partial success in one patient. The right eye improved markedly, but the increasing chemosis and progressive protrusion of the left eye, which was more seriously involved, failed to respond satisfactorily. X-ray therapy to the pituitary gland was not tried in this case because our limited experience with it at this hospital has not been encouraging. At the suggestion of Dr. M. C. Sosman several advanced cases in our clinic have been treated by irradiation directly to the orbit. Thus far the results have been impressive, but the series of cases is too small to warrant further comment. The hope of developing an ideal treatment for this condition lies, of course, in a thorough understanding of all of the major factors which promote its development. Until more is known of these, one should avoid thyroidectomy in those cases which look suspicious preoperatively. If one is confronted, for one reason or another, with the necessity of subjecting to operation a patient who falls into this category, it would be a wise precaution to administer desiccated thyroid in addition to iodine preoperatively in order to prevent the development of at least one condition, viz., hypothyroidism, which is known to affect the eyes of such individuals adversely.

SUMMARY

The anatomical and physiological aspects of experimental exophthalmos in lower mammals have been correlated with the clinical picture of exophthalmos in man. Included in these studies were observations on the position of the eyeball in man during stimulation of the cervical sympathetic chain. Of the various possible explanations for the mechanism of exophthalmos in Graves' syndrome, it is suggested that edema of the orbital tissues is the most likely.

It has been concluded that the exophthalmos in Graves' syndrome, like that of the guinea pig injected with an extract of the anterior pituitary gland, goes through two phases, the reversible and the irreversible. The former is that which is ordinarily encountered in exophthalmic goiter; the latter is that which infrequently occurs as a post-thyroidectomy complication of patients with this disease or rarely may actually precede the development of hyperthyroidism. The evidence also suggests that an exophthalmos-producing (ophthalmotropic) factor in the pituitary gland, which is distinct from the thyrotropic hormone, induces both types of exophthalmos. The nature of this ophthalmotropic activity of the pituitary is unknown. The use of the word *ophthalmotropic* does not imply that a specific chemical substance having this physiological action is believed to exist as such in the pituitary gland. The fact that it probably is directly or indirectly responsible for edema of the orbital tissues suggests that it may be tied in with the important rôle which the pituitary plays in regulating water metabolism.

Certain circumstances apparently predispose patients with exophthalmic goiter to the development of the irreversible type of orbital pathology. The most important of these is thyroidectomy; another is sex; and there are probably others. The loss of thyroid

function through thyroidectomy may make its influence felt in one or more of several ways. It could remove an important normal inhibitor of unbridled pituitary function, the result of which would be an increased secretion of thyrotropic and ophthalmotropic substances. It is also conceivable that the thyroid hormone collaborates closely with the pituitary gland in maintaining a proper body water balance and that thyroidectomy upsets this integrated control of water metabolism.

Essentially two types of cases of Graves' disease are encountered clinically, viz., special eye cases and the classic goiter syndrome. Suggestions have been made for the detection and treatment of the small group of cases which develop the serious ocular complications of Graves' disease.

REFERENCES

1. Whitnall, S. E.: The Anatomy of the Human Orbit and Accessory Organs. Oxford University Press, London, 1921.
2. Müller, H.: *Ztschr. f. Wissensch. Zool.* 9: 541. 1858.
3. Bernard, C.: Leçon sur la physiologie et la pathologie du système nerveux. Paris, J.-B. Baillière et Fils, 1–2: 499. 1858.
4. Sappey: *Arch. gén. de méd.* 121: 104. 1868.
5. Harling, Th.: *Ztschr. f. rat. Med.* Third Series 25: 275. 1865.
6. MacCallum, W. G., and W. B. Cornell: *Med. News.* 85: 732. 1904.
7. Code, C. F., and H. E. Essex: *Am. J. Ophth.* 18: 1123. 1935.
8. Essex, H. E., and W. C. Corwin: *Am. J. Ophth.* 20: 153. 1937.
9. Wagner, R.: *Ztschr. f. rat. Med.* Third Series. 5: 331. 1859.
10. MacCallum and Dandy: consult MacCallum and Cornell (6).
11. Troell, A.: *Arch. Int. Med.* 17: 382. 1916.
12. Jonnesco, T.: Sect. Physiol. XIII. Cong. Internat. de Méd. Paris. p. 26. 1900.
13. Friedgood, H. B., R. B. Cattell and W. P. Beetham: (unpublished data).
14. Friedgood, H. B., and S. Bevin: *Am. J. Physiol.* 125: 153. 1939.
15. Hogben, L.: *Proc. Roy. Soc. Ser. B.*, 94: 204. 1922–23.
16. Spaul, E. A.: *Brit. J. Exper. Biol.* 1: 313. 1923–24 and 2: 33. 1924–25.
17. Schwartzbach, S. S., and E. Uhlenhuth: *Proc. Soc. Exper. Biol. & Med.* 26: 153. 1928.
18. Loeb, L., and R. B. Bassett: *Proc. Soc. Exper. Biol. & Med.* 27: 490. 1930.
19. Loeb, L., and W. J. Siebert: *Proc. Soc. Exper. Biol. & Med.* 27: 495. 1930.
20. Schockaert, J. A.: *Proc. Soc. Exper. Biol. & Med.* 29: 306. 1931.
21. Loeb, L., and H. Friedman: *Proc. Soc. Exper. Biol. & Med.* 29: 172. 1931.
22. Friedgood, H. B.: *J.A.M.A.* 100: 1521. 1933; *Bull. Johns Hopkins Hosp.* 54: 48. 1934.
23. Marine, D., and S. H. Rosen: *Proc. Soc. Exper. Biol. & Med.* 30: 901. 1933.
24. Ruedemann, A. D.: *J.A.M.A.* 97: 1700. 1931.
25. Gley, E.: *Compt. rend. Soc. de biol.* 1: 858. 1910.
26. Marine, D., and S. H. Rosen: *Am. J. Med. Sci.* 188: 565. 1934.
27. Thomas, H. M., and H. C. Woods: *Bull. Johns Hopkins Hosp.* 59: 99. 1936.
28. Soley, M. H.: Paper presented at the 25th Annual Meeting of the Association for the Study of Internal Secretions.
29. Friedgood, H. B.: *Arch. Int. Med.* 56: 833. 1935.
30. Werner, S. C.: *Proc. Soc. Exper. Biol. & Med.* 34: 390. 1936.
31. Werner, S. C.: *Proc. Soc. Exper. Biol. & Med.* 34: 392. 1936.
32. Hertz, S., R. H. Williams and J. H. Means: *Trans. Am. Assoc. Study of Goiter* (in press).
33. Rawson, R. W.: Personal communication.
34. Aird, R. B.: *Arch. Ophth.* 24: 1167. 1940.
35. Smelser, G. K.: *Am. J. Ophth.* 20: 1189. 1937 and 22: 1201. 1939.
36. Paulson, D. L.: *Proc. Staff Meeting, Mayo Clinic.* 14: 828. 1939.
37. Hertz, S., R. H. Williams and J. H. Means: *J. Clin. Investig.* (in press).
38. Marine, D., and S. H. Rosen: *Proc. Soc. Exper. Biol. and Med.* 35: 354. 1936–37.
39. Friedenwald, J. S.: *Ann. Surg.* 96: 995. 1932.
40. Moore, R. F.: *Lancet.* 2: 701. 1920.
41. Thomson, E. S.: *Am. J. Opth.* 7: 27. 1924.
42. Burch, F. E.: *Minnesota Med.* 12: 668. 1929.
43. Naffziger, H. C.: *Ann. Surg.* 94: 582. 1931; *Arch. Ophth.* 9: 1. 1933; *J.A.M.A.* 99: 638. 1932.
44. von Zalka, E.: *Beitr. z. path. Anat. u. z. allg. Path.* 92: 239. 1933.
45. Haines, S. F.: *Endocrinology* 12: 55. 1928.
46. Thompson, W. O., P. K. Thompson, A. G. Brailey and A. C. Cohen: *Am. J. Med. Sci.* 179: 733. 1930.
47. Thompson, W. O., and P. K. Thompson: *J. Clin. Investigation* 5: 441 and 471. 1928.
48. Friedgood, H. B.: *J. Pharmacol. and Exper. Therap.* 51: 134. 1934 and 53: 46. 1935.
49. Friedgood, H. B.: *Endocrinology* 20: 526. 1936.
50. Means, J. H.: The Thyroid and Its Diseases. J. B. Lippincott Co. p. 376. 1937.
51. Hertz, S., and J. H. Means: *Trans. Am. Assn. Study of Goiter*, p. 140. 1937.

Gonadotropic Hormone: Urine Assays during the Menstrual Cycle in Normal Women

[Gonadotropic Cycle]

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CLINICIANS HAVE LONG LOOKED to the laboratory for aid in objectively differentiating and classifying the various endocrinopathies involving the pituitary gland and the gonads. After the reliability of the Aschheim-Zondek and Friedman tests for pregnancy was established, it was hoped that gonadotropic assays of urine and blood would yield similar aid in diagnosis of gonadal dysfunctions. But the first prerequisite of any biological test proposed as a diagnostic and therapeutic aid in dysfunctional states is a thorough understanding of the range of values encountered in the normal individual. Since the research laboratories unfortunately have not supplied this prerequisite for normal gonadotropins, the clinician has been disappointed.

Two conditions must be met in order to provide the clinician a useful diagnostic tool. The first is that methods be sufficiently quantitative and sensitive to determine the normal levels of hormone excretion. The second is that the characteristics of the normal range be sufficiently distinct to provide a dependable index of abnormality.

It is undoubtedly true that no method for concentration of gonadotropic hormone, a procedure essential in a study of its excretion in normal women, will give 100% recovery of the hormone, and that any biological assay technic is fraught with the dangers inherent in animal variability. But improvements and simplification of the extraction methods, and improved animal assays have overcome to a large degree the handicaps of the earlier workers.

The aims of the present study were to determine the normal pattern of urinary gonadotropin excretion and its deviations in a group of young women, and thus to help ascertain whether the second requirement of a competent biological test can be satisfied, that is, the distinct and somewhat limited character of normal values which provides an adequate and simple base for comparison with abnormal states.

Since 1931 when Frank, Goldberger and Spielman (1) demonstrated the presence of a gonadotropic factor in the blood of nonpregnant normal women, various workers have reported their ability or inability, depending on the sensitivity of their methods, to detect this hormone in the urine or blood during the menstrual cycle (2–15). Until recently, even those who reported positive results found that the amount of gonadotropic hormone was large enough to be detected only on one or two days, usually near the middle of the cycle. With more sensitive methods, D'Amour (10), von Hamm and Rothermich (14) and Werner (15) have shown that this hormone is present in the urine at other times during the menstrual cycle. Kurzrok (4) and later D'Amour (10, 13) associated the peaks of gonadotropin excretion with the occurrence of ovulation.

The Heller and Heller modification of the original Zondek alcohol precipitation method has been found to yield better quantitative results than any other available method used in this laboratory, and is an adequate and comparatively simple technic for routine or large scale analyses of urine samples (16). The immature rat uterus method has been amply demonstrated to be sensitive and reliable (17). With these two technics, work has progressed from a study of the relative amounts of gonadotropic hormone excreted in women of all ages (18), to an investigation of the levels of excretion in men of various ages (19), and thence to the present study of periodicity of urinary gonadotropins during the normal menstrual cycle.

MATERIALS AND METHODS

For this study, daily urine samples were collected from 19 normal young women for a total of 22 normal

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complete menstrual cycles. The subjects' ages ranged from 19 to 37 years. The majority were students and nurses. Their menstrual histories were entirely normal, their cycles ranging from 22 to 34 days. The only menstrual complaint was slight dysmenorrhea on the first day of menstruation in 5 of the subjects. Complete 12-hour night specimens of urine were collected from 17 of 19 subjects. Complete 24-hour specimens were collected from the remaining 2 cases in which 2 consecutive cycles each were studied. The tropic hormone present in the urine excreted in 12 hours.

Since it was deemed most desirable to obtain positive stimulation in the assay animals in every day of the cycle when possible, the entire 12-hour volume of each day was injected into one rat, in order that the actual base line of excretion might be drawn. The limitations of such a procedure are fully realized, but it appeared preferable to injecting smaller amounts into a series of animals, with the inevitable result that

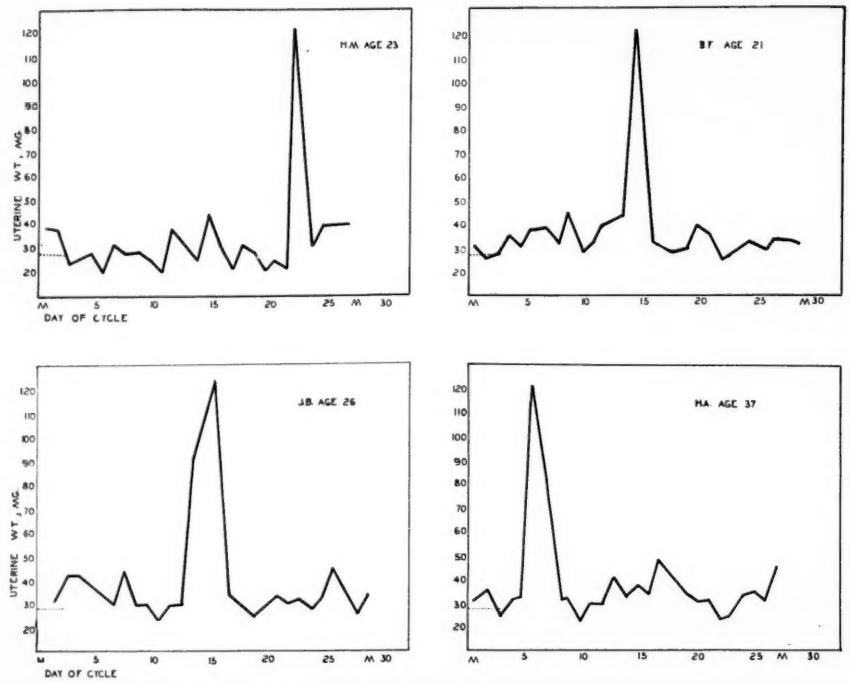

Fig. 1. Showing the cyclic character of gonadotropin excretion of the single peak type. The cycle of *A.F.*, age 24, which has not been included in the graphs is very similar to the cycle of *H.M.*, the gonadotropin peak occurring on the 24th day. The short dotted line on the ordinates indicates the level of minimal uterine weight increase.

samples were kept on ice during collection, and in the ice chest thereafter. The total 12-hour volume, and in the case of the 24-hour samples, one-half the 24-hour volume was precipitated with alcohol, the precipitate dried, washed with ether, and the hormone dissolved in water. Toxic salts in the solutions were removed by dialysis; reprecipitation with alcohol followed, and the precipitate taken up in 6 cc. of tap water for injection. The details of the procedure were identical with those previously described (16, 19). Twenty-four-day-old rats were injected subcutaneously twice daily for 3 days with the extract of the 12-hour volume. Autopsy was performed on the fourth day. The response of the rat was to the amount of gonado- the majority of the samples would have been completely negative. In the 4 cycles in which 24-hour samples were collected, each day's sample was divided into 2 and the concentration method applied separately to each half, and assayed on 2 rats. There was thus a check on the method of concentration as well as on animal variation. The results were surprisingly favorable. Out of 135 such daily samples for which there were 135 daily checks, in only 6 cases was there any considerable disagreement, 2 of these being due to partial loss of the solution in the checks. Since gonadotropic assays cannot be claimed to be more than roughly quantitative in any event, it therefore seemed justifiable to rely on the response of

one rat in order to allow detection of the hormone in as many days as possible.

The extract was remarkably non-toxic; in no case did a rat die as the result of the injection of the equivalent of a total 12-hour specimen, and there were only a few instances of toxic reactions in the animals. Those that occurred usually resulted from the injection of specimens obtained during the menses.

The results of the determined gonadotropic activity are based on the hormone content of urine collected over a 12-hour period expressed in terms of the uterine weight response of the rats. In some subjects where the urines were so potent that the response was beyond the maximal accurate uterine weight response, the ovarian weights have been used to express the activity. In these subjects, it was found that the amount of urine necessary to cause minimal ovarian weight increase was approximately twice as great as that necessary to cause minimal uterine weight increase. In other words, the uterine-ovarian weight ratio was 1:2. The urines whose potency is expressed in terms of ovarian weights are thus roughly twice as active as those whose potency is expressed in terms of uterine weights. The control uterine weight at autopsy of rats used in this laboratory is 21.6 mg. The control ovarian weight is 12.0 mg. The weights range from 18.0 to 26.7 mg. in the case of the uterus, and from 8.8 to 16.2 mg. in the case of the ovaries. Any uterine weight above 28 mg. and any ovarian weight above 18 mg. was arbitrarily considered indicative of gonadotropic stimulation.

It should be pointed out that the method of expressing gonadotropic activity of the urine differs in this study from that in the preceding studies. In the preceding work the standard of reference was the titer, the minimal volume of urine necessary to cause minimal uterine weight increase in the rats. In this study the approximate activity of the specimens could not be predicted in advance because of the cyclic nature of excretion in menstruating women. And since the amount of hormone was limited in each daily sample an accurate daily assay curve could not be made. The titer therefore is not applicable as a means of expressing the amount of hormone present in each daily urine sample from normal women. For this reason 12-hour excretion has been used as the standard of reference and the gonadotropic potency

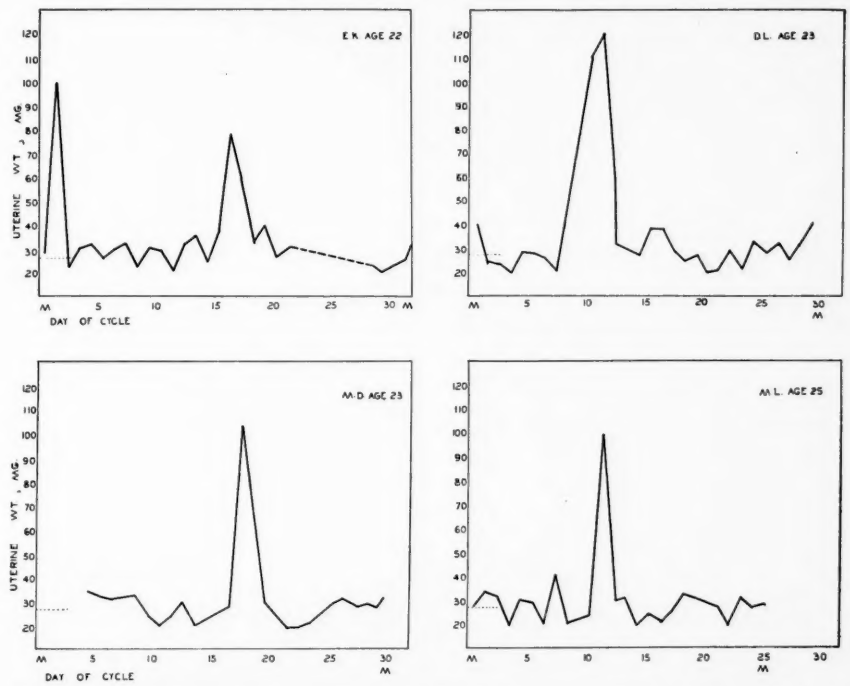

Fig. 2. SHOWING THE CYCLIC CHARACTER OF GONADOTROPIN EXCRETION OF THE 1 AND 2 PEAK TYPE. The cycle of *F.U.*, age 24, which has not been included in the graphs is very similar to *M.L.*, the gonadotropin peak occurring on the 10th and 11th days. The short dotted line on the ordinates indicates the level of minimal uterine weight increase.

has been expressed in the uterine and ovarian weight response.

RESULTS AND DISCUSSION

The data are represented graphically in figures 1 through 5. Gonadotropic hormone was demonstrable in the urine at some time during the menstrual cycle in all the normal women. In 5 of the 22 cycles it was detectable on every day of the menstrual cycle. In 2 subjects it was not demonstrated on 4 days; in 4 cases it was absent for 9 days. In the remainder of the series it was not present for from 5 to 11 days of the 28 to 32-day cycle. Definite and marked increases or peaks in the level of excretion occurred on at least one day of each cycle in all subjects but one. Analysis of the days of the menstrual cycle on which the increases in urinary gonadotropin occurred revealed that the greatest number of peaks appeared on the 12th, 13th and 15th days after the beginning of menstruation. However, in the various subjects there were peaks in the excretion level on almost any day of the menstrual cycle up to the 24th day. For instance, there were large increases in the excretion rate on the first and fourth days of the cycle of *M.M.* (fig. 3), and the only definite peaks in gonadotropin in the cycles of *H.A.* and *H.M.* (fig. 1) occurred on the sixth and seventh days, and on the 22nd day, respectively. It is interesting to note that with the exception of the cycle of *M.M.* (fig. 3) in which there was a small peak on the 26th day (4 days before the beginning of menstruation), there were no marked increases in hormone excretion from the 24th day to the start of the menses. On the contrary, many of the cycles (*E.H.*, *E.J.*, *D.H.*, and *R.B.*) showed a definite diminution in excretion as the cycle neared its end.

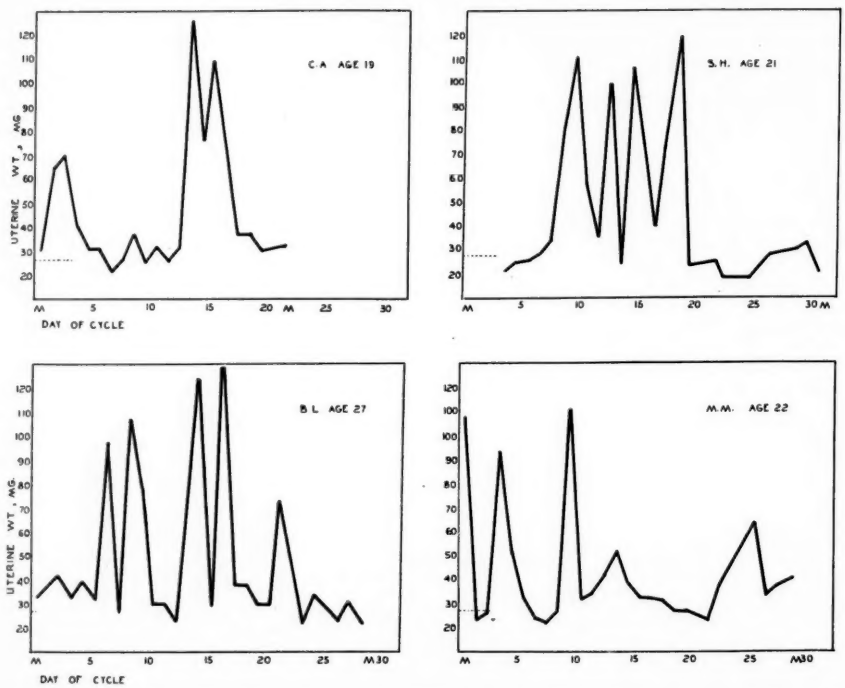

FIG. 3. SHOWING THE CYCLIC CHARACTER OF GONADOTROPIN EXCRETION OF THE MULTIPLE PEAK TYPE. An incomplete cycle of a subject not included in this series was similar to that of *B.L.*, increases over the base level of excretion occurred on the 10th, 11th, 14th and 19th days. The short dotted line on the ordinates indicates the level of minimal uterine weight increase.

In 11 of the 22 cycles there was just one marked peak in the level of gonadotropin excretion. It occurred on only one day, as in *B.F.* (fig. 1), or spread out over 2 or 3 consecutive days, as seen in the case of *J.B.* (fig. 1). In 5 of the subjects, the cycles were characterized by two to four distinct increases in hormone excretion of greater or lesser magnitude, occurring at various times during the menstrual cycle. The cycle of *B.L.* (fig. 3) serves to illustrate this point. On the seventh day after the beginning of menstruation, there was a marked rise in the potency of the urine specimen evidenced by the uterine and ovarian weight increase in the assay animal. A second peak

occurred on the ninth and tenth days, the ovarian weight response showing this peak to be of greatest magnitude. A third rise above the base level of excretion took place on the 15th, 16th and 17th days, and a fourth, of smallest magnitude on the 22nd day of the cycle.

One subject, *M.V.* (fig. 4) showed no distinct increase above a very low base level of gonadotropic hormone elimination. In this girl, all positive assays were but slightly above minimal, and the hormone could not be detected on 11 out of 31 days. On the seventh, and eighth days, and on the thirteenth, fourteenth days, and fifteenth which showed up in the ovarian weight response of the assay rats. The same phenomena were observed in the other four cycles which were from two young women who collected samples for two consecutive cycles (*D.H.* and *R.B.*; fig. 5).

In all four of these cycles the excretion rate was comparatively low on the first two days of menstruation, rose to unusual heights, and fell to the low level on the seventeenth and eighteenth days of the 26 and

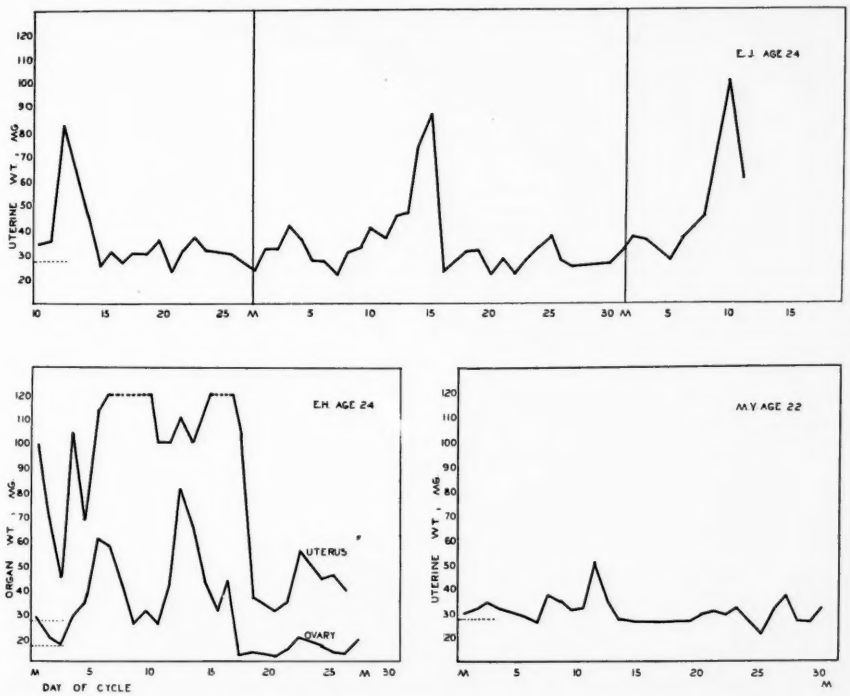

Fig. 4. Excretion pattern of gonadotropin through 2 consecutive cycles in a young woman is shown in the upper block. The cycle in the lower left hand corner exhibits very high excretion levels. Both uterine and ovarian weights are given for comparison. The 4th cycle shows a low rate of excretion with only a small increase on the 13th day. The short dotted lines on the ordinates indicate the levels of minimal uterine and ovarian weight increase.

thirteenth day, a small increase in urinary gonadotropin occurred as compared to the preceding and succeeding days, but it was not of the magnitude observed in the majority of the cycles.

An almost continuous high rate of excretion from the first few days of bleeding to the 20th to 25th day of the cycle characterized five of the menstrual cycles. *E.H.* (fig. 4), whose base level of excretion from the first to the twentieth days was approximately equal to that of most of the other women at the height of their peaks of excretion, had 2 marked increases superimposed upon this high base level on the sixth, 27-day cycles of *D.H.*, and on the twenty-third and twenty-fourth days of the 32 and 34-day cycles of *R.B.* In each cycle the middle period of continuous high excretion of gonadotropin has several peaks superimposed which were evidenced by the ovarian weight response of the rat. In both girls the levels of excretion in the second cycle closely followed the time relationships and magnitudes of the preceding cycle. In these 5 cycles since the urines were so potent, the uterine weight deviations lost their significance and the ovarian weight response expresses the levels of urinary gonadotropin in the graphs. In the case of *E.*

H. the uterine weight figures are also given. In the 4 cycles diagrammed in figure 5, the dotted lines represent the approximate uterine weight figures so that the comparison with the rest of the series may be better visualized. The amounts excreted by these 3 apparently normal young women were thus several times over the amounts excreted by any of the other subjects. The base levels of gonadotropin elimination up to the week preceding menses were frequently of about the same magnitude as the excretion peaks in the other cycles. On the basis of our results with menopause patients (18), if these urines had come from women exhibiting some symptoms of the menopause, the cases would have been considered members of the group designated as 'Transitional,' that is, as showing beginning ovarian failure. There was no outward evidence that this is true in any of the subjects. All 3 still have regular cycles; pelvic examinations on two revealed normal conditions and vaginal smear tests on all three were normal.

It is interesting to note in the three subjects in which two consecutive cycles each were studied, that the pattern of excretion of the succeeding cycle closely paralleled the time relationships and the amount of gonadotropin eliminated in the preceding cycle. Two of these cases were discussed above (*D.H.* and *R.B.*, fig. 5). The third subject, (*E.J.*, fig. 4), shows one peak in urinary gonadotropic hormone in both cycles, on the twelfth day in the first cycle and on the fourteenth day in the second. The hormone was excreted at a relatively constant low rate throughout the remainder of the period in both cycles. It would be necessary to study more subjects over longer periods before definite conclusions could be drawn, but it seems probable from the above cases and those of others (13, 15), that an individual's own pattern of excretion of hormone is usually adhered to rather closely in succeeding cycles. The reader is referred to the recent excellent paper by Werner (15).

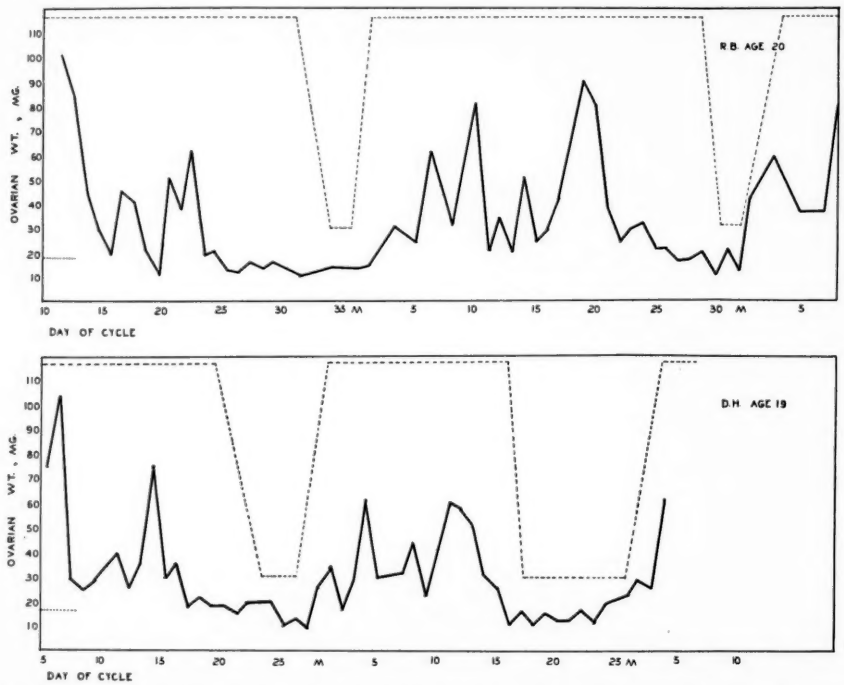

Fig. 5. Excretion pattern through 2 consecutive cycles in 2 young women. It was necessary to resort to the ovarian weight figures to represent the cyclic character of excretion since the potency of the urines was so high. The dotted lines diagram the approximate uterine weight figures. The short dotted lines on the ordinates indicate the level of minimal ovarian weight increase.

The range of normal values of urinary gonadotropin during the menstrual cycle as measured by the uterine and ovarian weight response of the rat may be seen from the graphs. With the exception of the 5 cycles described, the base levels of excretion in all other cycles may be considered of approximately equal magnitude. Even in the women showing a high rate of excretion, the base level of the other cycles was approached as the date of beginning menses was neared. What significance, if any, should be attached to the magnitude of the increases in excretion is not

known. The gonadotropin peaks in this series range from the almost negligible one in the cycle of *M.V.* (fig. 4), to the more common medium high peaks as illustrated in the cycles of *B.F.*, *H.A.*, *E.K.*, and *M.L.* (fig. 1, 2). At the other extreme of the range of values are the large peaks superimposed on the high excretion levels in the 5 cycles of *D.H.*, *R.B.*, and *E.H.* (fig. 4, 5).

The results of urinary gonadotropin tests on these 19 normal young women show therefore that the pattern of periodic excretion may vary from a very low output of hormone with no definite increases in excretion to a very high almost sustained output throughout the middle of the cycle, with apparently almost any conceivable pattern of peak excretion in between. It would appear then that there is no one definite pattern of excretion which may be classified as normal. Rather it would seem that any pattern of excretion as long as it falls within the wide limits of normal amounts must for the present necessarily be classed as normal. The normal values shown in this series ranged from barely detectable amounts to amounts comparable to those found in women showing beginning ovarian failure, which are, however, definitely below the menopausal or postmenopausal levels. It is true that the majority of excretion patterns were of one type, that is a relatively constant low level of urinary gonadotropin with one definite rise lasting from 1 to 3 days. But the time of appearance of the peak was not constant; it occurred anywhere from the sixth to the twenty-fourth day of the cycle. Also, there is no known reason for considering the other cycles as aberrant or abnormal.

In view of the variability in the pattern of gonadotropic hormone excretion in normal young women, it appears unlikely that urinary gonadotropin determinations will be of any diagnostic or differentiating value except in the extremes of gonadal dysfunction. In a young woman with a history of amenorrhea the absence of detectable amounts of urinary gonadotropin in 12-hour samples over a period of a week would be strong evidence in favor of amenorrhea of hypopituitary origin. On the other hand, amenorrhea accompanied by hyperexcretion of gonadotropic hormone is clear cut evidence of premature menopause or its beginning. The test has been used in this laboratory as an aid in distinguishing these two types of amenorrhea.

One of the significant points which has been proposed in connection with gonadotropic hormone excretion in normal females is that the sudden striking appearance of this hormone in the urine observed when using less sensitive assay methods very probably indicates the occurrence of ovulation (4, 10). The rationale behind such an assumption is not entirely clear, but it would seem to be that either the pituitary suddenly releases an excess of gonadotropic hormone which has its effect on the mature ovum and is then excreted through the kidneys, or that the changing relationship between the relative amounts of FSH and LH, which might presumably take place at this time is more effective on the end-organs of the assay animal (13). Kurzrok (4), who originally proposed the theory, used the earlier crude methods, and found gonadotropic hormone on one day near the middle of the cycles. Since much indirect and some direct evidence has indicated that ovulation does take place at about this time, the connection seemed obvious.

Later, D'Amour (10) using a more sensitive method found, as was the case in this study, that there are some cycles in which two or three peaks in gonadotropin excretion occurred. He interpreted these to mean that multiple ovulation took place in these women. In a more recent study, D'Amour (13) in an attempt to obtain more accurate assays for each day's sample has decreased his dosage per rat and used a larger series of animals. In doing this he has rendered his method less sensitive, and has erased the multiple peaks in excretion as well as the base level. He then found one definite increase in excretion per cycle, or no gonadotropin peak at all. D'Amour has reversed his multiple ovulation theory and he has suggested that one gonadotropin peak per cycle is indicative of ovulation, and that cycles in which there are no discernible amounts of gonadotropin are anovulatory. Small dose levels erased the base level and smaller peaks in excretion and allowed the increases of greatest magnitude to stand out significantly. But the existence of the hormone in amounts large enough for the detection of its daily presence, and to show other definite increases in excretion when using more sensitive methods, minimizes the importance of the urinary gonadotropin peak as indicative of ovulation. However, it seems somewhat more probable, as both D'Amour and Werner have suggested, that the time relationships between the urinary estrogen peak and the gonadotropic increase may be of special significance. In any event, final proof of the relationship between gonadotropin excretion peaks and ovulation must await direct and not indirect evidence.

There are three possible explanations of the periodicity of urinary gonadotropin which is manifested in the response of the assay animal. The pituitary may periodically release an excess amount of gonadotropic hormone which is then excreted in the urine. Secondly, the changing relative amounts of FSH and LH released by the pituitary may be a significant factor in the response of the assay animal. Studies conducted in this laboratory (20) have indicated that the rat uterus is sensitive to varying combinations of the two substances. With a subminimal constant dose of

FSH, increasing increments of LH will cause stimulation and increasing uterine weight response up to a maximum weight increase. The converse is also true using a constant and subminimal amount of LH. The third possibility is that the level of excretion of gonadotropic hormone is an index of the amount of hormone used or metabolized by the gonads, the pituitary merely releasing a continuous and fairly constant amount of hormone into the blood. Data from hormone assays and animal experimentation which would fit such a theory has been accumulating in this laboratory, and evidence has recently come from the work of Seidlin (21). He has shown that greater amounts of injected gonadotropic hormone are excreted by castrated guinea pigs than by intact animals, and that gonadotropic hormone is partly removed from solution when brought into contact with saline suspensions of ovarian tissue. He has suggested that the gonads permanently withdraw the gonad-stimulating hormone from the blood. His work is as yet unconfirmed. However, our results of gonadotropic assays in human urine are in accord with this possibility. In menopause and castrate women, and in castrate and eunuchoid men where large quantities of gonadotropins are excreted it may be that, since the gonads are inactive or absent, no hormone is metabolized and it therefore accumulates in the blood and is excreted in large amounts. In young men and women, and in many old men smaller amounts are excreted possibly because the gonads are removing the hormone from the blood. The cyclic character of urinary gonadotropin in menstruating women could be interpreted as cyclic activity and inactivity of the ovaries in using a constant supply of gonadotropic hormone.

SUMMARY

Urine assays of gonadotropic hormone during 22 complete menstrual cycles from 19 normal young women revealed that the hormone is excreted at low levels throughout the menstrual cycle. Cyclic appearance of increased amounts occurred in all but one case. However, the pattern of periodic excretion of urinary gonadotropin varied greatly not only as to the time relationships, but also as to the number of peaks and their magnitude. In 3 subjects high levels of excretion were sustained throughout the cycle until the fourth week. Three women whose urines were assayed through 2 consecutive cycles followed closely their preceding excretion patterns in the second cycle. It was concluded that there is no distinct pattern of gonadotropin excretion which may be classed as normal. Rather it appears that any pattern of excretion as long as it falls into the wide limits of apparently normal values must be classed as normal. In view of the variability of periodic excretion, it appears unlikely that urinary gonadotropin determinations will be of any clinical diagnostic value except in the extremes of gonadal dysfunction. The possible correlation between gonadotropin excretion and ovulation, and possible mechanisms concerned in the character of excretion are discussed.

The author wishes to express her appreciation of the helpful assistance and advice of Dr. E. L. Sevringhaus and Dr. C. G. Heller.

REFERENCES

1. Frank, R. T., M. A. Goldberger and F. Spielman: *Proc. Soc. Exp. Biol. & Med.* 28: 999. 1931.
2. Zondek, B.: *Klin. Wchnschr.* 10: 221. 1931.
3. Katzman, P. A., and E. A. Doisy: *Proc. Soc. Exp. Biol. & Med.* 30: 1188. 1935.
4. Kurzrok, R., I. J., Kirkman and M. Creelman: *Am. J. Obst. & Gynec.* 28: 319. 1934.
5. Albright, F.: *New Eng. J. Med.* 212: 192. 1935.
6. Frank, R. T., and U. J. Salmon: *Proc. Soc. Exp. Biol. & Med.* 32: 1237. 1935.
7. Smith, G. Van, and O. W. Smith: *New Eng. J. Med.* 215: 908. 1936.
8. Palmer, A.: *Proc. Soc. Exp. Biol. & Med.* 37: 273. 1937.
9. Frank, R. T., M. Goldberger, U. J. Salmon and G. Felshein: *J.A.M.A.*, 109: 1863. 1937.
10. Dripps, Della, and A. Osterberg: *Endocrinology* 23: 703. 1938.
11. D'Amour, F. E., D. Funk and H. Liverman: *Am. J. Obst. & Gynec.* 37: 940. 1939.
12. Bagby, B. B.: *J. Lab. Clin. Med.* 25: 687. 1940.
13. D'Amour, F. E.: *Am. J. Obst. & Gynec.*, 40: 958. 1940.
14. von Haam, E., and N. O. Rothermich: *Proc. Soc. Exp. Biol. & Med.* 44: 369. 1940.
15. Werner, S. C.: *J. Clin. Invest.* 20: 21. 1941.
16. Heller, C. G., and E. J. Heller: *Endocrinology* 24: 319. 1939.
17. Heller, C. G., H. D. Lauson and E. L. Sevringhaus: *Am. J. Physiol.* 121: 364. 1938.
18. Heller, C. G., and E. J. Heller: *J. Clin. Invest.* 18: 171. 1939.
19. Heller, E. J., C. G. Heller and E. L. Sevringhaus: *Endocrinology* 29: 1. 1941.
20. Heller, C. G., and H. D. Lauson: Unpublished Data.
21. Seidlin, S. M.: *Endocrinology* 25: 696. 1940.

Relation of Dose and Type of Estrogen to Nausea and Vomiting

[Stilbestrol]

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THERE IS A WIDE DIVERGENCE of opinion both as to the incidence and the cause of nausea and vomiting following the administration of stilbestrol. The incidence of reactions has varied widely in reports by different authors, some reporting an incidence as low as 5%, others as high as 80%. The various methods claimed to diminish or obviate these reactions, such as administering the substance in powdered form in milk, in enteric coated pills, in gelatin capsules or with bile acids, do not seem logical. Since nausea and vomiting are also produced by parental administration of stilbestrol it is unlikely that such reactions are caused by a local effect in the gastro-intestinal tract. We have also observed such reactions in a few patients given the substance by inunction.

A detailed review of the many reports on stilbestrol is beyond the scope of this article. There is, however, a fairly good correlation between the size of the dosages used by the various authors and the incidence of reactions which they have reported. In general, the authors who have used the higher doses have obtained a higher incidence than those who have used lower dosages. Shorr, Robinson and Papanicolaou (1), however, concluded that "there is no relation between the size of the dose and the development of toxic reactions." More recently Mazer, Israel and Ravetz (2) presented evidence that there is a definite relationship between the size of the dose and the incidence of reaction.

The object of this communication is to present evidence which confirms the findings of these latter authors. This evidence was obtained from a group of 283 menopausal patients observed since January 1939, and given oral or parenteral stilbestrol and related stilbene derivatives.

Oral Stilbestrol. Stilbestrol has been administered orally to 127 menopausal patients. The daily dose has varied from 0.1 to 2.0 mg. These amounts have been sufficient to control and maintain the patients symptom-free. The average necessary daily dose was approximately 0.5 mg. These doses are smaller than those reported by most observers, particularly those who reported a high incidence of reactions.

The term 'necessary dosage' as used by us refers to the amount required to relieve the menopausal symptoms and does not refer to the state of the vaginal smear. In common with other observers we have found little or no correlation between the dosage necessary for symptomatic relief and that required to cause estrous changes in the vaginal mucosa. The objective of therapy in menopausal patients is the relief of symptoms. Discussion of necessary dosage should therefore refer to the amounts necessary to attain this objective rather than the amounts capable of stimulating the vaginal mucosa. This matter of necessary dosage has been mentioned since it seems probable that oral stilbestrol has been innocuous in our hands because we have endeavored to give amounts no larger than necessary.

Of a total of 127 patients only 13 (10.2%) have complained of reactions following its use. Eight-tenths % had nausea and vomiting, and 9.4% nausea only. Figure 1 shows what % of these 13 reactions occurred at the various dosage levels. The findings

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that *a*) no reactions followed administration of 0.1 mg., *b*) 1 followed 0.33 mg., *c*) 4 followed 0.5 mg., and *d*) 8 followed 1.0 or 2.0 mg. are not significant in themselves. If very few patients had been given the lower doses it would be impossible to obtain more than a very few reactions. This, however, was not the case. In the figure the number of times each dose has been administered is shown as the percentage of the total number of administrations. Thus, while 48.3% of all doses administered fell in the low dosage range of 0.1 to 0.33 mg., only 7.6% of the reactions followed these dosages. On the other hand, the high

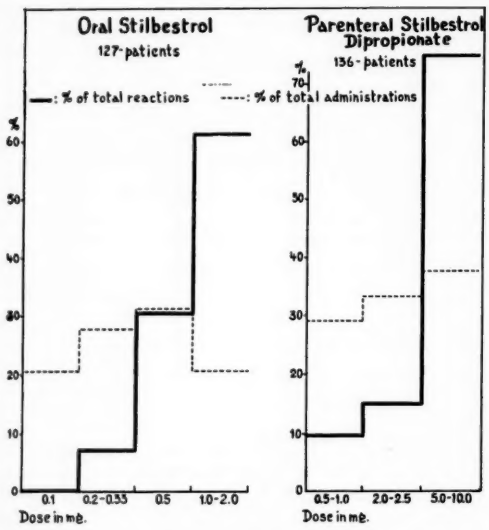

Fig. 1. REACTION OF PATIENTS TO ORAL STILBESTROL AND TO PARENTERAL STILBESTROL DIPROPIONATE.

doses of 1.0 to 2.0 mg. were given relatively infrequently (20.5% of all doses administered), but caused 61.5% of the reactions. From these findings it is evident that there is a direct relationship between the size of the dose of oral stilbestrol and the incidence of reactions.

The importance of the size of the dose in producing reactions is further emphasized by the fact that in at least 11 of the 13 patients the reactions were probably due to overdosage. In each of these 11 we subsequently determined that doses ½ to 1/20 as large were adequate to control the menopausal symptoms. With these smaller doses no reactions were provoked.

Parenteral Stilbestrol Dipropionate. Stilbestrol dipropionate has been administered intramuscularly to 136 menopausal patients. Of these, 14.7% (20) reported reactions; 11.76% suffered only nausea and 2.94% reported nausea and vomiting. Figure 1 shows the distribution of reactions in the various dosage groups. As with oral stilbestrol the reactions were more frequent with the higher dosages. Only 25% of the reactions occurred in the lower dosage groups of 0.5 to 1.0 mg. and 2.0 to 2.5 mg., although 62.4% of the total administrations were in this dosage range. Seventy-five % of the reactions followed doses of 5.0 to 10.0 mg., while only 37.6% of all treatments were of this magnitude.

Parenteral Stilbestrol. Twenty-five patients who had been receiving parenteral stilbestrol dipropionate were given identical milligram amounts of parenteral stilbestrol. None of these particular patients had shown reactions to the stilbestrol dipropionate. Following the stilbestrol 24% of these patients complained of nausea and vomiting and another 28% complained of nausea alone (total reactions 52%). We realize that this is a higher incidence than has been reported by most other observers. The primary object in giving the parenteral stilbestrol was to compare its estrogenic effectiveness with that of stilbestrol dipropionate. Accordingly relatively high doses of the stilbestrol were given (1.0–10.0 mg.; average 5.24 mg.) and this fact may explain the high incidence of reactions.

Estrified estrogens are slowly absorbed from the injection site and have a prolonged effect. Free estrogens such as stilbestrol or estrone, on the other hand, are relatively more rapidly absorbed and their duration of effect is consequently shorter. Due to their more rapid absorption the blood stream concentration during the first 2 or 3 days after injection is higher with the free than with the esterified forms. The greater blood stream concentration after administration of free stilbestrol is probably the explanation for the greater reaction incidence. There is actually a larger amount of circulating estrogen in the early period following the free stilbestrol injection and thus more nausea and vomiting than after stilbestrol dipropionate.

COMMENTS

The data presented in this paper demonstrate a direct correlation between the size of the dose and the incidence of reactions following both oral stilbestrol and parenteral stilbestrol dipropionate. Reactions were more frequent with the higher dosages and less frequent with the smaller dosages. These data represent observations on fairly large groups of patients, 127 in the oral stilbestrol group and 136 in the stilbestrol dipropionate group. In some reported studies a correlation between dosage and reactions probably has not been apparent for one or both of two reasons. Either too few patients were studied or only the higher dosages were given and thus the lesser incidence of reactions with the smaller dosages was not observed.

With parenteral therapy the incidence of nausea

and vomiting is affected by the absorption rate as well as by the actual number of milligrams administered. The number of reactions is high with stilbestrol, which is relatively rapidly absorbed from the injection site and thus achieves a relatively high blood stream concentration in the early post-injection period. Reactions are less frequent with stilbestrol dipropionate which is relatively slowly absorbed from the oil depot and causes a lower blood stream concentration although one of more prolonged duration.

Oral stilbestrol effectively controls menopausal symptoms, and when properly administered, should not cause reactions. Proper administration entails the avoidance of amounts which are in excess of the individual needs of the patients. The dose necessary to control symptoms varies to a very large degree between different patients and cannot be accurately predicted. If administration of stilbestrol is therefore started at a low dose in all patients and increased slowly and gradually as is necessary to relieve symptoms, reactions will not occur.

Such a procedure has been used in approximately half of our patients (those who had not previously been receiving parenteral therapy). Treatment was started with a dosage of 0.1 mg. daily. After one or usually 2 weeks, the dosage was increased to 0.2 mg. if there had been no symptomatic improvement. After each succeeding 1 or 2 week intervals, the dose was raised to 0.5, 1.0, 1.5, and 2.0 mg. as necessary until the symptomatic response was obtained and maintained. This technic entails a fairly long period of time before symptoms are relieved in some patients. Only 22.5% of our patients, however, needed doses larger than 0.5 mg. (calculated from 98 patients whose minimal necessary dose has been established as accurately as possible). The disadvantage of the technic in these few patients, however, is completely outweighed by the fact that none of the patients treated in this manner suffered undesirable side reactions.

The stilbestrol dipropionate was furnished by Lakeside Laboratories, Milwaukee, Wisconsin. Stilbestrol was furnished by the Lakeside Laboratories, Milwaukee, Wis., by Eli Lily and Co., Indianapolis, Indiana, and by the Allen Laboratories, New Brunswick, New Jersey.

REFERENCES

1. Shorr, E., F. E. Robinson and G. N. Papanicolaou: A clinical study of the synthetic estrogen stilbestrol. *J.A.M.A.* 113: 2312. 1939.
2. Mazer, C., C. L. Israel and E. Ravetz: The synthetic estrogen stilbestrol. *J.A.M.A.*, 116: 675. 1941.

Effect of Desoxycorticosterone Acetate on Glucose Tolerance in Normal Individuals and in Patients with Addison's Disease[1]

[Adrenals and Glucose Tolerance]

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DESOXYCORTICOSTERONE HAS BEEN RECOGNIZED as the most effective of the cortical adrenomimetic steroids so far used in the treatment of adrenalectomized animals and patients with Addison's disease (1, 2). However, certain toxic manifestations and its apparently limited influence upon carbohydrate metabolism have tended to restrict its judicious application to human beings. It is the purport of the present study to show that large doses can be used for relatively long periods of time in the management of the disease without untoward effect, provided adherence to certain rules is observed. Moreover, data relative to variations in blood glucose levels under varying conditions are presented in detail to suggest the rôle that desoxycorticosterone may be capable of playing in intermediary carbohydrate metabolism.

METHODS

Diet. Before beginning the tests, normal subjects and patients with Addison's disease were maintained for 7 to 21-day periods on diets in which the proportions of carbohydrate, protein and fat were kept constant. Control subjects were given a daily intake of carbohydrate 350 gm., protein 100 gm., and fat 150 gm. Patients with Addison's disease received approximately 7 gm. of carbohydrate, 1.6 gm. of protein and 2.5 gm. of fat per kg. of body weight. The sodium and potassium intake of the diets was calculated at all times. Diets containing 1.5 gm. of sodium and 7 gm. of potassium were used in 2 patients and 8 controls. A third patient and each of 3 controls ingested 3 gm. of sodium and 4.5 gm. of potassium daily. In the case of the normal subjects, salt *ad libitum* was added to the diet until the administration of desocycorticosterone was begun.

Oral glucose tolerance test. A routine meal of 100 gm. of glucose was employed for all tests. Blood samples were taken hourly over 5 to 6-hour periods of time. Desoxycorticosterone acetate, when employed, was given at the same time on test as on other days, except in instances later to be noted. While the use of the oral route of administration is open to some criticism, it was felt that in the present instance a better concept of general improvement in the patient's condition could be obtained by paying some attention to variations in absorption as well as to factors concerned with intermediary metabolism.

Other data. Cardio-thoracic ratios were determined from 2-meter roentgenograms of the chest taken at the end of inspiration. Weights and blood pressures were observed at corresponding hours on successive days. Serum sodium and potassium were estimated from fasting blood specimens by the methods of Hawk and Bergeim (3) and of Rappaport (4) respectively.

RESULTS

Fasting blood glucose. In 11 patients with Addison's disease, the average fasting blood glucose (37 deter-

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minations) was 74.5 mg. %, and ranged between 60 and 95 mg. %. In 6 patients under treatment with desoxycorticosterone acetate and fully stabilized on the hormone, the average fasting blood sugar (57 determinations) was 79.1 mg. %, with a variation from 57 to 117 mg. %. Fasting blood sugar levels appeared to be unaffected by the administration of desoxycorticosterone acetate.

Effect of desoxycorticosterone acetate upon glucose tolerance curves in normal subjects. Glucose tolerance tests were made on 11 male subjects before and after the daily injection of 15 mg. of desoxycorticosterone acetate in oil for a period of one week.[2] These were divided into 2 groups. Eight of the men received, in addition to the standard test diet, 1.5 gm. of sodium and 7 gm. of potassium daily. Their ages averaged 30.1 years, their height, 178.5 cm., and their weight, 81.3 kg. Blood pressures were within normal range throughout the experimental period, but showed an average maximum reduction of 20 mm. of Hg. during the first 3 days of sodium restriction and desoxycorticosterone acetate administration, returning to the former level before the end of the period. Fluctuations in weight were not significant. In the second group were 3 males with an average age of 53 years; weight, of 65.1 kg., and height of 158 cm. In addition to the standard test diet 3 gm. of sodium and 4.5 gm. of potassium daily was given to each of them. In both groups dietary factors and salt ingestion were kept constant throughout the preliminary period and the period of testing. The results are given in detail in table 1 and are summarized graphically in figure 1.

TABLE 1. GLUCOSE TOLERANCE TESTS BEFORE AND AFTER THE USE OF DESOXYCORTICOSTERONE ACETATE

Patient	Age	Time	Blood glucose (mg. per 100 cc.) hourly					
			0	1	2	3	4	5
		Na 1.5 gm.; K 7 gm. daily						
M.H.	22	before	96	170	148	125	80	74
		after	86	170	100	70	79	84
R.K.	28	before	77	142	124	81	95	98
		after	83	175	94	77	77	84
R.O.	23	before	56	83	89	53	65	54
		after	75	114	68	36	58	64
J.R.	23	before	87	164	100	71	77	
		after	84	243	98	76	58	55
J.T.	22	before	90	131	99	49	87	73
		after	84	166[1]	108	38	48	68
N.T.	44	before	85	135	110	100	90	88
		after	82	140	110	100	88	93
J.G.	38	before	77	128	100	95	84	80
		after	76	135	90	90	88	76
A.M.	41	before	84	130	120	95	86	80
		after	81	152	122	70	68	82
		Na 3 gm.; K 4.5 gm. daily						
A.B.	56	before	100	160	130	100		
			105	130	145	95	105	
		after	100	180	110	85	80	
M.C.	43	before	80	100	110	100	90	
			90	135	120	90	80	
		after	86	130	115	100	70	
J.C.	56	before	75	155	110	95	93	
			94	125	125	110	110	
		after	95	165[1]	130	90	80	

[1] Urine 0.5% sugar.

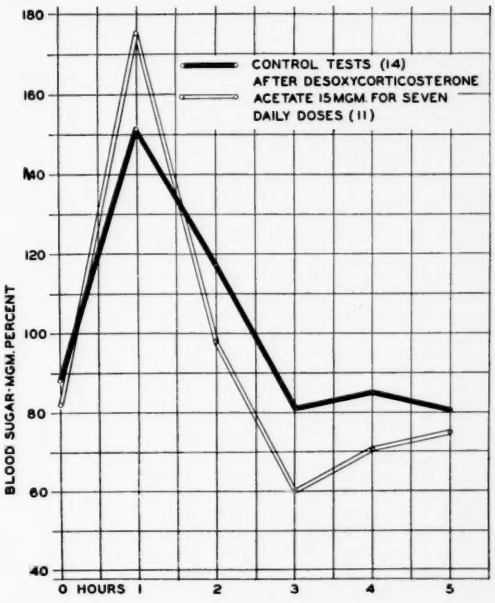

Fig. 1. ORAL GLUCOSE TOLERANCE CURVES IN NORMAL SUBJECTS BEFORE AND AFTER RECEIVING DESOXYCORTICOSTERONE ACETATE.

Correlation of data in patients with Addison's disease. Three patients with fully proven Addison's disease served as the basis for the study. Pertinent data are summarized in table 2.

The very low values for blood glucose in the initial glucose tolerance curves were the result of at least 2 factors, a lack of adreno-cortical hormone, and the poor absorptive power of the intestinal tract.

Following treatment with a daily intake of 9 gm. of sodium and 5 mg. of desoxycorticosterone acetate for 2 weeks, and of 3 gm. of sodium and 15 mg.

[2] The desoxycorticosterone acetate in oily suspension for injection, and the sterile compressed tablets for subcutaneous implantation employed in this and subsequent studies were furnished by Dr. Max Gilbert, of The Schering Corporation, Bloomfield, N. J.

desoxycorticosterone acetate for an additional 3 weeks, *patient J.F.* showed an increase in weight, blood pressure, cardiothoracic ratio, and blood sugar levels. Blood serum sodium was still low and his diarrhoea had not improved. The fact that these two factors failed to respond to treatment leads to the conclusion that the improved blood sugar levels, well sustained through the fourth hour, must have been due to a direct action of the adreno-cortical hormone its equivalent by subcutaneous implantation. On this regime his absorptive blood sugar levels rose moderately, and his blood serum sodium, cardiothoracic ratio, blood pressure and weight attained normal values.

On increasing the desoxycorticosterone acetate to 8.5 mg.[3] daily, the early part of the sugar tolerance curve was further elevated, whereas from the fourth hour on it was significantly depressed. After decreas-

Table 2. GLUCOSE TOLERANCE AND SERUM Na AND K STUDIES IN 3 PATIENTS TREATED WITH DESOXYCORTICOSTERONE ACETATE.

Week	Diet (gm.) C	P	F	Na	K	Hormone Daily[2]	Wt. (kg.)	B.P.	C.T.R.[3]	Serum (mg. %) Na	K	Glucose Tolerance (Hr.) (mg. %) 0	1	2	3	4	5	6	Remarks
Patient J. F., age 60, ht. 160 cm.																			
1	Ward[1]					0	32.2	70/50	0.38	302	28	65	90	65	90	88	68		14–18 stools daily
6	Variable			9	4.5	5S	33.2	80/60	0.44	312	22								Treatment begun 5th week. Condition same.
9	350	100	150	3	4.5	15S	36.0	95/65	0.43	303	19	107	124	113	104	87			Diarrhoea
11	350	100	150	3	4.5	20S	36.0	100/70	0.45	327	16	70	85	130	85	80			Stools normal
13	350	100	150	3	4.5	25S	41.6	116/72				84	100	105	90	90			
14	350	100	150	3	4.5	25S	41.7	148/84	0.51	332	16	80	95	100	105	80			
Patient K. K., age 24, ht. 153 cm.																			
2	Variable			11	2	20E	41.8	96/50	0.32	265	10	92	106	65	60				
14	Variable			11	2	20E	47.7	120/80	0.42	341	14	78	100	70	64				
20	Variable			11	2	5S	50.0	140/80	0.40	382	13	80	102	80	60				
36	Variable			11	4	5S	50.0	130/82	0.41	405	18	60	110	62	70				
48	Variable			6	4	2.5I	51.0	118/80		328	19	78	115	130	90	85	75		
98	350	100	150	6	4	4S 1.5I	51.5	100/60	0.40	269	16	93	165	124	97	60	51	61	Previous treatment until 3 wks. ago
99	350	100	150	1.5	7	15S 1.5I	52.0	90/72		267	12	71	81	60	94	30	41		Shock at 5th hr. Relief from glucose
100	350	100	150	1.5	7	20S 1.5I	54.0	108/64	0.43	299	14	61	96	91	92	60	48	49	
101	350	100	150	1.5	7	25S 1.5I	54.3	130/96		273	13	62	130	107	55	35	35	60	Urine Cl as NaCl 1.9 gm. 24 hr.
102	350	100	150	1.5	7	30S 1.5I	54.9	126/92	0.50	284	15	58	150	121	128	40	75	70	
Patient E. M., age 42, ht. 165 cm.																			
0	—	—	—	—	—	—	51.0	66/55	0.33	288	26	60	94	88	62				
8	Ward[1]			12	2	10S	53.6	130/70	0.46	448	12	70	110	84	80	63			
28	Variable			6	4	5S	53.8	124/80	0.42	308	20	88	130	120	100	100	107		5 days after U.R.I.[4]
36	Variable			6	4	2.5I	57.2	120/75		328	19	80	100	88	90				Treatment as before until 3 wks. ago
85	350	100	150	1.5	7	10S	58.6	114/78		345	16	83	133	98	103				
87	350	100	150	1.5	7	15S	58.6	120/70	0.41	400	17	83	154	103	79	121	100	90	
88	350	100	150	1.5	7	20S	58.4	150/70	0.42	391	11	71	93	70	105	—	51	111	
89	350	100	150	1.5	7	25S	59.1	140/72	0.42	279	12	82	90	87	74	50	67	57	
90	350	100	150	1.5	7	30S	59.0	164/120	0.48	313	12	93	160	127	106	125	74	78	Headache and edema disappearing 2 days
91	350	100	150	1.5	7	30S	59.4	158/88	0.46	310	13	77	135	117	144	122	100	70	Urine Cl as NaCl 1.6 gm./24 hr.

[1] Yields between 2000 and 2200 calories, with C, 250; P, 100; F, 90 (approximately).
[2] E, watery extracts; S, desoxycorticosterone acetate, suspension in oil; I, pellet implants, calculated daily absorption.
[3] Cardiothoracic ratio.
[4] U.R.I.—upper respiratory infection.

rather than to greater intestinal absorption or an increased salt action. On increasing doses of hormone, all features of the patient's clinical condition steadily improved to normal, except for the blood glucose levels which, following the administration of a test meal, receded to lower levels as the daily dose of hormone was increased. The significance of these findings will be discussed later.

Patient K.K. (table 2, fig. 2) has been studied for approximately 2 years, during the first 22 months of which he received daily 6 to 9 gm. of sodium, 4 gm. of potassium, and from 5 to 7.5 mg. of the suspension of desoxycorticosterone acetate intramuscularly or ing the sodium ingestion to 1.5 gm. daily, and gradually raising the dosage of steroid to 33 mg. daily, the sugar tolerance curve was at first flat throughout. By the end of the fourth week normal blood sugar values were obtained in specimens up to 4 hours. The depression at the fourth hour was followed by subsequent low normal levels at the fifth and sixth hours. These values for blood sugar were attained while the serum sodium still remained depressed, 124 m. eq per

[3] Each milligram absorption from implanted material is deemed equal in activity to 3 milligrams of injected hormone. This statement holds only for pellets obtained from the source used throughout these studies.

liter. On the other hand, the cardiothoracic ratio and body weight were normal for the first time on these high doses of hormone.

Determinations made upon *patient E.M.* (table 2) at the 28th week of observation showed a balanced effect of 6 gm. of sodium and 5 mg. of steroid daily upon sugar tolerance, cardiothoracic ratio, blood pressure and weight, despite a slightly lowered serum sodium. After an acute infection, blood sugar values were lowered throughout the test period. Towards the end of the second year, this patient was placed for 9 weeks on a diet of carbohydrate 350 gm., protein 100 gm., fat 150 gm., sodium 1.5 gm., and potassium 7 gm. The daily dose of hormone was gradually raised during this period from 10 to 30 mg. The behavior of the glucose tolerance curves is recorded in table 2, and in figure 3. The well sustained curve seen with a dose of 15 mg. of desoxycorticosterone acetate a day gave way to hypoglycemic variations with doses of 20 mg. and still further depression when 25 mg. doses were administered. Simultaneously, the blood pressure approached hypertensive levels. Following the administration of 30 mg. of desoxycorticosterone

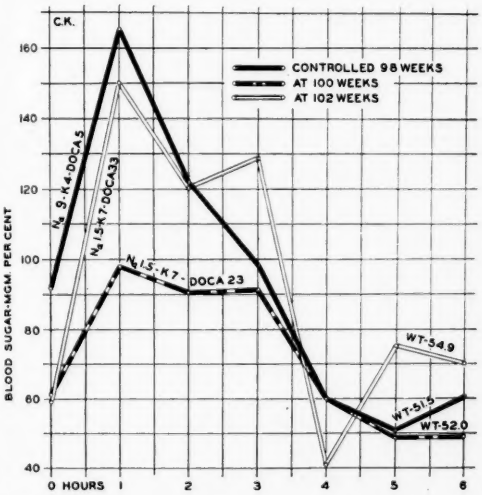

Fig. 2. ORAL GLUCOSE TOLERANCE TEST IN CONTROLLED ADDISON'S DISEASE. Effect of variations in Na, K, and desoxycorticosterone intake.

acetate daily for 3 days, the hypertension was definite, recurrent headaches were present and very slight transient ankle edema appeared. At the same time blood sugar levels after a test meal were normal. The hypertension and accompanying signs disappeared spontaneously while the dosage of the hormone and the previous salt intake were constant. The blood sugar curve assumed the proportions of those seen in normal individuals. Subjectively the patient stated that he "has not felt so well in 12 years."

Despite the low salt intake during the latter weeks of observation, it will be noted that a satisfactory chloride balance was maintained by both *patients K.K. and E.M.* (table 2).

The curve of reciprocal relationship between optimum sodium intake and optimum dose of desoxycorti-

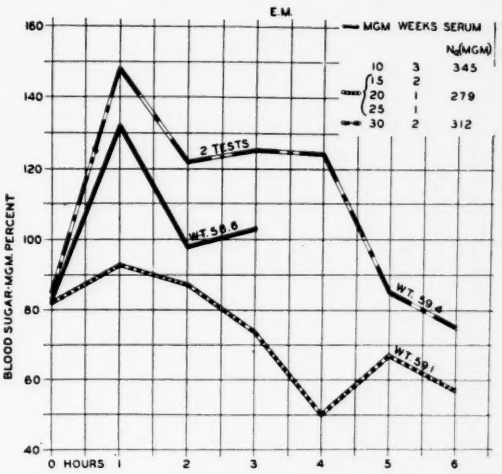

Fig. 3. ORAL GLUCOSE TOLERANCE TESTS. Effect of varying dosage of desoxycorticosterone in patient with Addison's disease receiving a diet of carbohydrate 350; protein 100; fat 150; Na 1.5; K 7; expressed in grams.

costerone acetate. Six patients with Addison's disease have been given varied amounts of sodium and desoxycorticosterone acetate. By trial and error, an optimum[4] amount of each of these has been determined in 21 instances. These optima have been charted in the accompanying figures (fig. 4). By substitution in the basic parabolic equation, $y=k/x$, a value of 45 for the constant k was found, when y represents the daily intake of sodium in grams, and x the daily dose of desoxycorticosterone acetate in milligrams. With these values, the formula may be written Na (gm.) $=45/D$ (mg.).

This apparently holds good as rule of practice within the limits noted in figure 4. If more than 12 gm. of sodium are used, the dosage of desoxycorticosterone acetate is then so small as to be ineffective. If more than 30 mg. of desoxycorticosterone acetate is employed, then the amount of sodium is too small to meet the needs of the body. Indeed, we are not yet sure that 1.5 gm. of sodium can be continued indefinitely although no ill effects have been noted over periods up to 9 weeks, at the end of which time the

[4] By the word 'optimum' in this connection we mean the relative amounts of sodium and steroid necessary to maintain a patient free of symptoms, gaining in weight, and with normal or 'near normal' values for blood pressure, cardiothoracic ratio, blood serum sodium, and blood sugar.

24-hour-output of chloride has indicated a satisfactory balance (table 2).

Obviously the state of function of the adrenal cortex will to some extent vary this rule, as is shown in the present preliminary data, all of which do not conform perfectly to the theoretical curve. Nevertheless the stated ratio creates a point of departure for each individual case and affords a definite plan of approach to the control of two of the important factors involved in the management of the patient with Addison's disease.

Potassium values cannot be ignored, but the present studies do not permit any generalization on this

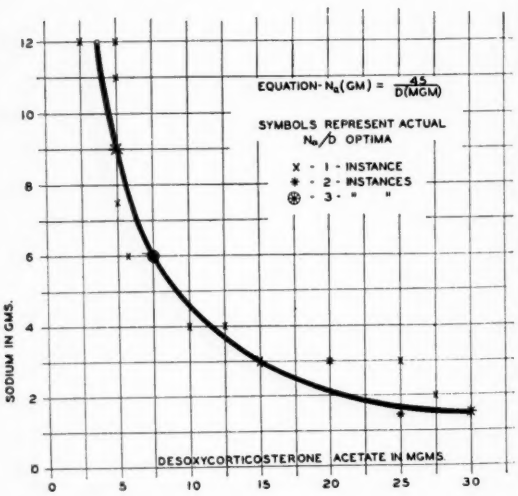

Fig. 4. Curve of optimum relation between Na ingestion and dosage of desocycorticosterone acetate.

point. To date it has been noted that all patients, receiving 15 or less mg. of desoxycorticosterone acetate daily, progress satisfactorily on the ratio normally present in the average diet. For higher doses of hormone, it has been the custom arbitrarily to raise the daily potassium intake to 7 gm., although we have no clinical proof that such an increase is necessary.

DISCUSSION

The low fasting blood sugar levels seen in patients with Addison's disease are directly attributable to inability of the individual with adreno-cortical insufficiency to produce sugar from protein or fat. It would appear from the present studies that desoxycorticosterone acetate does not restore this function. Lewis and his associates (5) have shown that adrenalectomized animals maintained "in good condition" on desoxycorticosterone show a limited ability to form glucose from lactic, pyruvic and glycogenic amino acids. Moreover, the ability of the drug to reestablish or to increase the glycosuria of adrenalectomized partially depancreatectomized dogs is limited (6). "This may indicate that the effective concentration of this substance required to influence carbohydrate metabolism is greater than that necessary to support adrenalectomized animals" (6). In other words, gluconeogenesis does not result directly from its administration. In this connection, Ferrebee (7) and his associates state that neither desoxycorticosterone acetate nor other closely related steroids exerts an effect upon protein metabolism as measured by changes in nitrogen excretion.

Evidence is not lacking that desoxycorticosterone acetate can exert an antidiabetic action (8, 9). This effect is strikingly transient, and is followed by a demand for as much insulin as before (8).

The blood-sugar-raising action of desoxycorticosterone acetate is much better known than the insulin-like action mentioned above. Many workers believe that it exerts a very favorable influence upon the disturbances in carbohydrate metabolism that occur in Addison's disease (10–15). Harrison and Harrison (10) found that desoxycorticosterone acetate "does prevent the drop in concentration of blood sugar found in untreated adrenalectomized rats." However, the amount required to exert this action was found to be much greater than that necessary to restore concentrations of serum electrolytes and non-protein nitrogen constituents to normal. Anderson (14, 15) has shown that, with the aid of desoxycorticosterone, the adrenalectomized animal handles carbohydrate foods in a manner similar to sham-operated controls.

In view of the studies of Thorn and his associates (16), the low fasting levels for blood sugar seen in the present group of patients with Addison's disease must be looked upon, at least in part, as a failure of this drug to play any important rôle in gluconeogenesis from protein and fat.

The rather slight elevation of the blood sugar following the ingestion of glucose in the untreated case of Addison's disease, or early in treatment with desoxycorticosterone acetate may be variously interpreted. Thorn (16) and associates have demonstrated that poor absorption from the intestinal tract is partly but not fully (17) responsible. The improvement in postprandial blood sugar levels in our *patient J.F.* (table 2), despite no change in his rather intractable diarrhoea, suggests that factors other than the intestinal resorption must be vitally concerned. On the basis of experimental evidence Wells (12) feels that not one of the adrenal cortex steroids is "essential for a specific chemical reaction which is suppressed in adrenalectomized animals." On the other hand, the carbohydrate regulating as well as other

effects are probably brought about "through the maintenance of the tissues so that they can carry out physiologic processes at rates which approach the normal."

Of all the steroids yet isolated or synthesized, desoxycorticosterone acetate has proven to be the most effective as a life maintaining material (2). As a part of its general influence upon nutrition of the cells must be placed whatever beneficial action it exerts upon carbohydrate metabolism. Apparently it lacks the specific blocking effect upon insulin which is characteristic of the ketosteroids that have an oxygen or hydroxyl group at carbon atom-11 (12). Therefore, it brings about a gradual change in carbohydrate metabolism by an indirect action (16). Such a conception accounts for the satisfactory condition of *patient J.F.* after 8 weeks of adequate treatment despite the continuance of a flat sugar tolerance curve. It does not so readily explain why in both *patients E.M.* and *K.K.*, 5 weeks and 3 weeks respectively after beginning relatively large daily doses of hormone, a nearly normal response was obtained to ingested glucose, whereas, later, with even larger doses of hormone, there was a very flat curve. We believe this sequence of events raises the question of the depressing action of desoxycorticosterone acetate upon the function of the adrenal gland, the pituitary gland or the liver.

Atrophy of the adrenal has been produced in rats by relatively large doses of the drug, 10 mg. daily for 20 days (18). This effect is, however, not specific for desoxycorticosterone acetate, as whole gland extracts and various other crystalline steroids have evoked a similar response (19, 20, 21). In view of these facts it is possible that a diminution in the function of the adrenal cortex does occur as a secondary response to the prolonged use of desoxycorticosterone acetate.

With such a decrease in adrenal function, a suppression of pituitary activity is known to occur in adrenalectomized animals (22), particularly if they are not protected by a high sodium intake. Moreover, such an effect, although not proven, may be possible in the case of desoxycorticosterone because of its estrone and progesterone-like effects (23–26). Both of these hormones are thought to bring about cyclic changes in the pituitary which may in turn depress hepatic function, or to give rise to a liver disturbance directly (27).

As increasing doses of desoxycorticosterone are administered to the 'stabilized' patient, there is at first a depression of the glucose tolerance curve, followed by a tendency for it to approach normal (table 2 findings in *patients E.M.* and *K.K.*) This may occur at or above the point of sodium-desoxycorticosterone acetate equilibrium represented by the equation $Na = 45/D$. If the former, then the explanation may lie in the fact that the patient is for the first time in complete satisfactory balance, for example *patient E. M.* On the other hand, the fact that nearly normal curves were not readily obtained until this equation was satisfied with large amounts of hormone and small amounts of sodium, and only rarely occurred in the reverse instance would seem to suggest that the synthetic material exerts either directly or indirectly some other action. In the light of a vast amount of experimental evidence the first possibility seems unworthy of serious consideration. That changes may take place in the hormone itself when relatively large quantities are present has not been investigated. The close chemical relationship between it and steroids with a proven effect upon gluconeogenesis makes this more than a bare possibility. Moreover, its gynecogenic action suggests a more than casual physiologic relationship with estrone and progesterone (23–26). Conversely, progesterone has been shown to be effective in maintaining adrenalectomized animals in good condition provided estrone is not present (26). It will also be noted that as the largest doses of the hormone are continued, the tendency to an increased blood pressure disappears. This raises the question as to whether conversion within the body into other steroids with different physiologic activity takes place.

The same question arises when we consider the influence of desoxycorticosterone on the blood sugar curves of normal subjects (fig. 1). The composite curve for the test period differs from that of the control by exhibiting an early higher rise and a marked depression approaching hypoglycemic levels in the fourth and fifth hours. It is difficult to explain these curves on a negative basis, that is on the basis that desoxycorticosterone does not influence factors concerned in carbohydrate metabolism. We believe the two features of the curve just mentioned represent a moderate depressing action of the drug upon that portion of the secretion of the adrenal gland concerned with the deposition of glycogen in the liver and with the formation of glucose from other sources than carbohydrate. This would account for the early high levels with one instance of glycosuria and for the later extremely low values. Moreover, such a variation in action may account for the seemingly paradoxical observations that desoxycorticosterone ameliorates diabetes (8, 9) and produces glycosuria (11, 12).

The influence of acute infection upon the glucose tolerance curve is well illustrated in the case of *patient E.M.* (36th week). The fact that patients with Addison's disease experience difficulty in mobilizing sugar during and after infections needs little reiteration.

While low blood pressure readings have been returned to normal with relative small doses of desoxycorticosterone, and a reciprocally large dose of

sodium, restitution of other factors has not been so complete (see table 2). Serum sodium may reach unusually high levels; heart size is not satisfactorily increased, and sugar tolerance curves remain relatively flat. On the other hand, on high doses of desoxycorticosterone acetate and concomitantly lower doses of salt, all of these approach normal limits. On present evidence the interests of the patient will be best served by a diet containing 2.5 to 3 gm. of sodium with an average amount of potassium (4–5 gm.) and the daily administration of from 20 to 15 mg. of desoxycorticosterone.

The justification for such large doses of hormone is discussed elsewhere (28, 29). The administration of large doses of desoxycorticosterone acetate has so frequently been attended by untoward symptoms that overemphasis upon the conditions under which such doses are here recommended seems impossible. Ill effects can be avoided provided the following precautions are observed. *a*). The amount of sodium in the diet must be carefully calculated and maintained at a constant predetermined level (30). *b*). Heart size should be studied before and during treatment with particular attention to upward changes in the cardiothoracic ratio (31). *c*). The clinician should be constantly on the alert for other signs of toxicity, the appearance of any one of which should call for diminution in dose. Significant manifestations, somewhat in the usual order of their appearance, are: increasing weakness despite treatment; *rapidly* increasing weight; a blood pressure within hypertensive levels; excessive values for blood sodium; edema of any part of the body; and any or all of the signs of cardiac failure. *d*). Some variation in the constant (k) applicable in any particular case may be noted, but from observations to date values between 37.5 and 45 are satisfactory in more than 80% (28, 29). *e*). It seems inadvisable for reasons already mentioned to use the values at the extremes of the curve in figure 4. It appears that best clinical results are to be attained, and control of the patient most easily maintained, when the sodium intake is kept within physiological limits, namely, between 3 and 6 gm. daily, with a reciprocally indicated dose of desoxycorticosterone acetate.

SUMMARY AND CONCLUSIONS

Observations have been made on the influence of desoxycorticosterone acetate upon the blood glucose levels of 8 normal subjects maintained on a diet of constant values for carbohydrate, protein, fat, sodium and potassium.

The responses of 3 patients with Addison's disease to the administration of varying amounts of sodium and desoxycorticosterone acetate are recorded as to the following particulars: general sense of well being; weight; blood pressure; cardiothoracic ratio; serum sodium and potassium; fasting and post-prandial values for blood glucose.

By the method of trial and error in 21 instances, a curve of the reciprocal relationship which should obtain between sodium intake and desoxycorticosterone acetate dosage has been constructed. This conforms within certain limits to a portion of a parabola represented by the equation $Na\ (gm.) = 45/D(mg.)$.

Desoxycorticosterone acetate is a safe and important therapeutic agent in Addison's disease, provided that reciprocally proportionate amounts of sodium are ingested and that the potassium intake is not lowered.

When salt intake is reciprocally controlled, relatively large doses of desoxycorticosterone acetate exert a favorable influence upon carbohydrate metabolism, but through no *direct* role in the conversion of endogenous protein to carbohydrate as shown by the blood glucose values observed between the 4th and 6th hours of the standard oral test used.

REFERENCES

1. Wells, B. B.: *Proc. Staff Meet., Mayo Clin.* 15: 294. 1940.
2. Ingle, D. J.: *Proc. Soc. Exper. Biol. & Med.* 44: 450. 1940.
3. Hawk, P. B., and O. Bergeim: Practical Physiological Chemistry, Blakiston, Philadelphia, 11th ed., p. 472. (Weinbach). 1937.
4. Rappaport, F.: *Klin. Wchnschr.* 12: 1774. 1933.
5. Lewis, R. A., D. Kuhlman, C. Delbue, G. F. Koepf and G. W. Thorn: *Endocrinology* 27: 971. 1940.
6. Long, C. N. H., B. Katzin and E. G. Fry: *Endocrinology* 26: 309. 1940.
7. Ferrebee, J. W., C. Ragan, D. W. Atchley and R. F. Loeb: *Endocrinology* 27: 360. 1940.
8. Winnett, E. B., J. W. Caldwell and J. E. Kahler: *J. Iowa M. Soc.* 30: 45. 1940.
9. Bloomfield, A. L.: *Bull. Johns Hopkins Hosp.* 65: 456. 1939.
10. Harrison, H. E., and H. C. Harrison: *Proc. Soc. Exper. Biol. & Med.* 42: 506. 1939.
11. Ingle, D. J., and G. W. Thorn: *Am. J. Physiol.* 132: 670. 1941.
12. Wells, B. B., and E. C. Kendall: *Proc. Staff Meet., Mayo Clin.* 15: 565. 1940.
13. Ingle, D. J.: *Proc. Soc. Exper. Biol. & Med.* 44: 176. 1940.
14. Anderson, E., and V. Herring: *Proc. Soc. Exper. Biol. & Med.* 43: 363. 1940.
15. Anderson, E., V. Herring and M. Joseph: *Proc. Soc. Exper. Biol. & Med.* 45: 488. 1940.
16. Thorn, G. W., G. F. Koepf, R. A. Lewis and E. F. Olsen: *J. Clin. Investigation* 19: 813. 1940.
17. Thorn, G. W., G. F. Koepf, D. Kuhlman and E. F. Olsen: *Am. J. Physiol.* 129: 480. 1940.
18. Selye, H., and C. Dosne: *Proc. Soc. Exper. Biol. & Med.* 44: 165. 1940.
19. Ingle, D. J.: *Proc. Staff Meet., Mayo Clin.* 13: 733. 1938.
20. Ingle, D. J., G. M. Higgins and E. C. Kendall: *Anat. Rec.* 71: 363. 1938.
21. Wells, B. B., and E. C. Kendall: *Proc. Staff Meet. Mayo Clin.* 15: 133. 1940.
22. Koneff, A. A., R. O. Holmes and J. D. Reese: *Anat. Rec.* 79: 275. 1941.
23. Selye, H.: *Am. J. Physiol.* 132: 522. 1941.
24. Salmon, U. J.: *Proc. Soc. Exper. Biol. & Med.* 41: 515. 1939.
25. Speert, H.: *Bull. Johns Hopkins Hosp.* 67: 189. 1940.
26. Corey, E. L.: *Am. J. Physiol.* 132: 446. 1941.
27. Selye, H.: *J. Pharmacol. & Exper. Therap.* 71: 236. 1941.
28. McGavack, T. H.: *J. Lab. and Clin. Med.* (In press).
29. McGavack, T. H.: *New Eng. J. of Med.* (in press).
30. Babcock, L. and McGavack, T. H.: *N. Y. Med. Col. Bull.* 4: 1941.
31. McGavack, T. H.: *Am. Heart J.* 21: 1. 1941.

Intensive Carbohydrate Therapy in Diabetic Patients with Manifest or Suspected Liver Disease

[Diabetes and Liver Disease]

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THE IMPORTANT RÔLE OF THE LIVER in carbohydrate metabolism, first demonstrated by Claude Bernard, has been reviewed recently by one of us (1). It is generally recognized that the glycogen stores of this organ have an important bearing upon its functional integrity and upon its resistance to damaging agents, and wide use has been made of high carbohydrate therapy in liver disease (2). Recent work has clearly shown that the liver is a major factor in the maintenance of the normal blood sugar level. Diabetes mellitus may be regarded as a disturbance in this homeostatic regulation because of a relative lack of insulin or a relative excess of the opposing endocrine factors. The endocrine balance controls the level at which the liver regulates the blood sugar. Under these circumstances it is readily understandable that liver disease which interferes with the responsiveness of this organ to endocrine influences alters carbohydrate tolerance in the non-diabetic organism and decreases the effectiveness of administered insulin in the diabetic patient (3).

The present report deals with two groups of cases. Two diabetic patients who developed cholecystitis with liver damage were observed before and after surgical treatment combined with high carbohydrate therapy aimed at the liver damage. The dramatic improvement in carbohydrate tolerance which occurred in these patients following treatment directed our attention to another group of diabetic patients who were exhibiting unexplained loss of carbohydrate tolerance. It was suspected that these latter patients might have sub-clinical degrees of liver disease. Of these 6 patients, who presented themselves with unexplained losses of carbohydrate tolerance, 4 exhibited some evidence of mild liver disease and responded to intensive high carbohydrate therapy by a considerable improvement in carbohydrate tolerance. Of the 2 patients who gave no evidence of liver damage, 1 obtained a favorable result from the treatment, while the other did not.

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A. Diabetics with Cholecystitis and Liver Disease, Treated Surgically

Case 1. Anna S., a 66-year-old white housewife, entered the hospital with the diagnosis of acute cholecystitis of 2 weeks' duration. She was known to have had diabetes for a number of years but could not date its onset accurately. For about a year prior to admission she had been taking 25 U of protamine insulin daily, and it was evident that her knowledge of her diet was too vague for an accurate estimate. On admission she was given a diet of P 50, F 75, CHO 200, together with 25 U of protamine insulin daily. On this regimen her daily excretion of sugar varied from 2 to 6 gm. Her pre-operative treatment included the intravenous infusion of glucose for 11 days, and similar treatment was continued for 6 days post-operatively. In all she received 1,150 gm. of glucose intravenously in addition to her diet before operation, and 750 gm. of glucose in addition to the routine post-operative diet. At operation the gall bladder was found to be full of pus and stones and cholecystectomy was performed. Twenty days later she was discharged on a diet of P 70, F 50, CHO 200 with no insulin. Her urine was entirely sugar-free. At this time her blood cholesterol, which on admission had been 193 mg. % with 47% esters, was 210 mg. % with 63% esters and she was clinically well.

Case 2. Frieda S., a 53-year-old white housewife was admitted to the hospital with a story of recurrent attacks

of cholecystitis for about 8 months. At the time of admission she was recovering from a recent attack and was still icteric. She had been a known diabetic for 10 years and had first taken insulin 6 years prior to admission. At the time of onset of her cholecystitis, 8 months prior to admission, she was taking 15 U of regular insulin daily. With the recurrent attacks of cholecystitis the insulin requirement increased until, on admission, she was taking 50 U of regular insulin daily.

The patient's fasting blood sugar on admission was 138 mg.%. She was continued on the amount of insulin she had been taking at home, and was started on a diet of P 70, F 40, CHO 150 gm., on which her maximum daily glycosuria was 7 gm. Twelve hundred grams of glucose with additional insulin as necessary was administered intravenously over a 5-day period prior to operation. Cholecystectomy was performed and a stone, impacted just proximal to the ampulla of Vater, was removed. She received 1,000 gm. of glucose plus insulin during the first 5 days after operation, and a diet of P 70, F 70, CHO 175 was established in progressive steps. On this diet she at first required as much as 85 U of insulin daily. However, her tolerance steadily improved, and 58 days after operation she required no insulin whatever, her urine was sugar-free and her fasting blood sugar was 139 mg. %.

B. Diabetics with Unexplained Loss of Carbohydrate Tolerance and Suspected Liver Disease, Treated Medically (Table 1)

Six diabetic patients were selected from the Mandel Clinic (outpatient) of the Michael Reese Hospital. Each had been followed in the clinic for many months or years and each had recently shown an unexplained progressive loss in carbohydrate tolerance. On admission to the Max Pam Unit for Metabolic Research of the Michael Reese Hospital the patients were given the insulin and diet last prescribed in the clinic. They were then observed for a period of at least 2 weeks, during which time the insulin dosage was adjusted until the diabetes was adequately controlled as judged by absence of glycosuria and the morning fasting blood sugar level. Following this period of stabilization a daily blood sugar curve was constructed by determining the blood sugar level just before each meal, 2 hours after each meal and just before bed-time. The insulin dosage was then decreased by 10 U and 3 or more days later the blood sugar curve was repeated. If this curve was as good as or better than the preceding one, the daily insulin dosage was again reduced by 10 U and the above procedure followed. When the reduction of the daily insulin dosage by 10 U of insulin resulted in a significantly worse daily blood sugar curve, the patient was considered to have made his maximum improvement under these conditions and was deemed ready for special treatment. It should be emphasized that the pre-treatment insulin requirements noted in table 1 were the minimal requirements under hospital conditions and after the usual initial spontaneous improvement in tolerance had been obtained.

The treatment consisted essentially of the administration of 300 to 350 gm. of additional glucose daily together with sufficient insulin to keep the blood sugar level in the neighborhood of the renal threshold at about 200 mg. %. Our aim was to maintain a high blood sugar level in the presence of adequate insulin for 12 hours daily over a period of at least a week. Thus by correcting the relative deficiency of insulin in our diabetic patients, we were attempting to apply the well known high carbohydrate treatment for liver disease commonly used in non-diabetics.

Five of the patients were given the additional glucose intravenously in the form of 10% glucose solution. To maintain salt and water balance, 1 l. of the infusing fluid was made with distilled water, while the other 2 were made with physiological saline. The 6th patient, whose superficial veins were difficult of access, received the extra 300 gm. of carbohydrate daily by mouth divided into hourly feedings from 8:00 A.M. to 10:00 P.M. In 3 of these 6 cases, in which we wished to avoid a change in body weight, the equivalent of 1,200 calories was omitted from the regular diet. In the other 3 cases the administered carbohydrate was in addition to the regular diet.

The daily procedure as regards the intravenous therapy was as follows. The patient received his regular dose of insulin and breakfast by 8:00 A.M. By 9:00 A.M. the intravenous infusion had been prepared and was started. The rate of infusion was adjusted to approximately 250 cc. per hour, so that the 3 l. which the patient was to receive would be delivered in the course of 12 hours. The dose of insulin upon which the patient had been stabilized was continued, and in addition regular insulin was mixed with the infusing fluid in amounts and at times indicated by qualitative sugar tests of the patients' urine throughout the day and the occasional determination of the blood sugar.

Blood sugar determinations were made by the Somogyi modification of the Shaffer-Hartman micro method. Bromsulphalein liver function tests were made as follows. Bromsulphalein, 5 mg./kg. of body weight, was injected into an ante-cubital vein and 30 minutes later blood was drawn from the ante-cubital vein of the opposite arm. Bromsulphalein content of the serum was determined by colorimetric comparison and retention of more than 15% was considered abnormal. For the oral hippuric acid test 6 gm. of sodium benzoate was given by mouth and the urine was collected for 4 hours. Excretion of 3 gm. (in terms of benzoic acid) was considered 100%. For the intravenous hippuric acid test 1.77 gm. of sodium

TABLE 1. RESULTS OF INTENSIVE CARBOHYDRATE THERAPY PLUS INSULIN IN DIABETICS

Before Treatment			During Treatment										After Treatment		
Diet	Insulin	Blood sugar	Day	1	2	3	4	5	6	7	8	9	Diet	Insulin	Blood sugar
gm.	u	mg. %											gm.	u	mg. %
Case 3, Christine S.															
P 60 F 70 CHO 150	25	7:30 A.M. 93 10:00 A.M. 113 11:30 A.M. 67 2:00 P.M. 105 4:30 P.M. 90 7:00 P.M. 107 9:30 P.M. 107	CHO[1] intake, gm. Glycosuria, gm. CHO retained Total insulin, u	440 18 422 25	440 6 434 50	440 4 436 50	440 2 438 50	440 4 436 50	440 2 438 50	440 22 418 50			P 60 F 70 CHO 150	0	7:30 A.M. 92 10:00 A.M. 112 11:30 A.M. 91 2:00 P.M. 95 4:30 P.M. 83 7:00 P.M. 117 9:30 P.M. 120
Case 4, Hyman C.															
P 100 F 120 CHO 300	40	7:30 A.M. 112 10:00 A.M. 184 11:30 A.M. 149 2:00 P.M. 152 4:30 P.M. 146 7:00 P.M. 190 9:30 P.M. 136	CHO[1] intake, gm. Glycosuria, gm. CHO retained Total insulin, u.	663 66 597 55	553 10 543 55	553 25 528 55	553 14 539 55	553 3 550 55	553 13 540 55	553 1 552 55			P 100 F 120 CHO 300	0	7:30 A.M. 96 10:00 A.M. 98 11:30 A.M. 97 2:00 P.M. 120 4:30 P.M. 144 7:00 P.M. 137 9:30 P.M. 107
Case 5, Goldie M.															
P 80 F 40 CHO 150	30	7:30 A.M. 87 10:00 A.M. 162 11:30 A.M. 82 2:00 P.M. 116 4:30 P.M. 71 7:00 P.M. 176 9:30 P.M. 149	CHO[1] intake, gm. Glycosuria, gm. CHO retained Total insulin, u.	440 5 435 30	440 1 439 30	440 4 436 30	440 1 439 30	440 9 431 25	440 6 434 25	440 1 439 25			P 80 F 40 CHO 150	0	7:30 A.M. 106 10:00 A.M. 166 11:30 A.M. 91 2:00 P.M. 145 4:30 P.M. 101 7:00 P.M. 170 9:30 P.M. 114
Case 6, Elsie J.															
P 110 F 170 CHO 140	50	7:30 A.M. 123 24-hr. urine sugar-free	CHO[1] intake, gm. Glycosuria, gm. CHO retained Total insulin, u.	489 18 471 50	489 28 461 50	489 12 477 50	489 36 453 50	489 32 457 50	489 2 487 50	489 12 477 50			P 110 F 170 CHO 140	25	7:30 A.M. 123 24-hr. urine sugar-free
Case 7, Fannie E.[2]															
P 80 F 75 CHO 175	65	7:30 A.M. 120 10:00 A.M. 152 11:30 A.M. 107 2:00 P.M. 206 4:30 P.M. 136 7:00 P.M. 202 9:30 P.M. 161	CHO[1] intake, gm. Glycosuria, gm. CHO retained Total insulin, u.	455 1 454 95	505 1 504 80	505 1 504 80	505 1 504 80	505 2 503 65	505 3 502 65	505 1 504 65					
			Day CHO[1] intake, gm. Glycosuria gm. CHO retained Total insulin, u.	8 505 2 503 55	9 505 3 502 55	10 505 2 503 55	11 505 1 504 55	12 505 5 500 55	13 505 2 503 45	14 505 2 503 45			P 80 F 75 CHO 175	30	7:30 A.M. 137 10:00 A.M. 168 11:30 A.M. 138 2:00 P.M. 168 4:30 P.M. 120 7:00 P.M. 161 9:30 P.M. 171
Case 8, Harry C.															
P 90 F 100 CHO 205	70 (40–0–30)	7:30 A.M. 17 10:00 A.M. 102 11:30 A.M. 76 2:00 P.M. 129 4:30 P.M. 56 7:00 P.M. 104 9:30 P.M. 70	CHO[1] intake, gm. Glycosuria, gm. CHO retained Total insulin, u.	567 53 514 70	567 77 490 70	567 56 511 80	567 66 510 90	367[3] 8 359 100	567 86 481 110	567 90 477 100	567 86 481 100	467[3] 25 442 110	P 90 F 100 CHO 205	70 (70–0)	7:30 A.M. 45 10:00 A.M. 168 11:30 A.M. 96 2:00 P.M. 176 4:30 P.M. 116 7:00 P.M. 155 9:30 P.M. 111

[1] Here, as in the case histories, the values for total carbohydrate intake include that administered as glucose plus the carbohydrate equivalent of the diet.
[2] In this patient the high carbohydrate therapy was administered orally, and was continued for 14 days.
[3] Solution reaction. Intravenous therapy stopped for the day and 2 extra days added.

benzoate in distilled water was injected intravenously and the urine collected in 1 hour. Excretion of 0.7 gm. (as benzoic acid) was considered minimal normal excretion (4).

For brevity in the presentation of case histories certain non-contributory facts will be omitted. Details as to the past menstrual and family history will be omitted unless they bear directly upon the diabetic status of the patient. Details of physical examination and laboratory work will also be omitted when they have no direct relationship to the problem at hand. Included in a 'normal' report of labora-

tory work are the following routine procedures done on all patients: blood Wassermann and Kahn tests; blood counts, red, white, hemoglobin and differential; blood N.P.N.; complete urine examination (excepting for sugar). None of our patients exhibited any evidence of infection.

Case 3. Christine S., a 50-year-old white housewife entered the hospital with diabetes known for 8 years. Fourteen years prior to admission the patient had had a sub-total thyroidectomy. Four years prior to admission insulin was first given and 2 years later the patient was taking 240 U of insulin daily. During a period of hospitalization at that time insulin was reduced to 25 U daily but no reason could be found for the change in tolerance. Two years later the diabetes was again out of control, and so the patient entered the hospital for the present study. A sister of the patient had diabetes. Physical examination on admission to the hospital revealed nothing remarkable except for obesity and a smooth liver edge palpable 1 cm. below the costal margin in the right mid-clavicular line. Routine laboratory findings were normal, except for 2+ albuminuria. Bromsulphalein tests both before and after treatment showed 35% retention. Blood cholesterol, 260 mg. % with 63% esters on admission was not repeated. Two B.M.R. determinations on separate occasions were +36 and +16 without signs of hyperthyroidism. Roentgenograms demonstrated a normal sella turcica.

The patient lost 9 pounds and weighed 158 pounds on discharge. The urine continued sugar-free for the 2 months during which we were able to maintain contact with the patient.

Case 4. Hyman C., a 44-year-old white unemployed male entered the hospital with glycosuria and acetonuria, and a story of diabetes known only for 1 month, during which time no insulin had been taken. Physical examination revealed an apparently normal although somewhat dehydrated patient. After acidosis had been overcome, the diabetes was controlled and the patient treated as the other patients in the series. Routine laboratory findings were normal. Blood total cholesterol was 445 mg. % with 71% esters and was not repeated. Bromsulphalein test showed 5% retention. Intravenous hippuric acid test gave 39% of minimal normal excretion on 2 occasions before treatment and 86% after treatment. Roentgenograms showed a normal sella turcica, and B.M.R. determinations on separate occasions were +3, −10 and −20.

The patient weighed 120 pounds on admission and the same when discharged. He has remained sugar-free without insulin to date (9 months).

Case 5. Goldie M., a 54-year-old white housewife was admitted to the hospital with diabetes known for 4 years and an insulin requirement which jumped from 0 one year prior to hospitalization to 40 U daily when admitted to the hospital. Three years prior to admission hyperthyroidism was suspected but not proved, despite B.M.R. ratings of +19 to +33. During the present study one basal metabolism test was −24, but there were neither signs of clinical thyroid disturbance, nor other physical findings of note. Routine laboratory findings were normal. Bromsulphalein test showed 5% retention and blood total cholesterol was 253 mg. % with 71% esters before treatment. Neither was repeated.

This patient lost 8 pounds in the hospital and weighed 145 pounds on discharge. Thereafter her urine remained sugar-free for 3 months without insulin. Then however, for an undetermined reason she exhibited glycosuria and had to be given insulin as before. Eight months after the above study she was again hospitalized because the diabetes was out of control and after 10 days of hospital management she was discharged with the above diet plus 20 U of insulin daily.

Case 6. Elsie J., a 48-year-old negro housewife entered the hospital with diabetes known for 5 years and an insulin requirement which had increased from 10 U daily when the diabetes was discovered, to 50 U daily on admission. The patient's father had diabetes. On admission the physical examination was noncontributory except for obesity, smooth enlargement of the thyroid gland and smooth firm liver edge, 2 cm. below the costal margin in the right mid-clavicular line. Routine laboratory findings were normal, except for a 2+ albuminuria. Visual fields, roentgenogram of the sella turcica, and neurological examination were all normal; B.M.R. was +1. Bromsulphalein test showed 40% retention on admission, but was not repeated.

The patient lost 6 pounds and weighed 201 pounds on discharge. For the next 3 months her urine was sugar-free on the 'after treatment' regime. She then left the city, disregarding both diet and insulin and when seen 3 months later the diabetes was again out of control.

Case 7. Fanny E., a 55-year-old white housewife, entered the hospital with diabetes known for 11 years, controlled without insulin until 3 years prior to hospitalization. She was then given 25 U of insulin daily, but by the time of admission she required 65 U daily. During this time her weight increased 15 pounds. The patient's mother, 2 aunts, and 3 brothers all had diabetes. Physical examination revealed obesity plus the presence of a nodule in the thyroid isthmus, but no evidence of disturbed thyroid function. The routine laboratory findings were normal. Blood total cholesterol was 404 mg. %, with 71% esters and 400 mg. % with 64% esters, on 2 occasions before treatment and 370 mg. % with 67% esters after treatment. Oral hippuric acid test before treatment was 148% of average normal excretion and after treatment 131%.[2] Basal metabolism determinations were 0, −10 and −15 on 3 occasions.

This patient varied only 2 pounds in weight throughout her hospital stay, and weighed 198 pounds at time of discharge. When seen 4 weeks later she was not adhering to the diet so that it was necessary to increase her insulin. Now, 7 months later, she has gained 14 pounds and requires 70 U of insulin daily.

Case 8. Harry C., a 45-year-old white unemployed male entered the hospital with diabetes known for 19 years, but controlled without insulin for 17 years. Two years prior to admission he required 50 U of insulin daily and at the time of admission he required 80 U daily. A brother

[2] It has recently been shown that hippuric acid excretions greater than 115% of the normal indicate early liver disease (5).

had diabetes. Physical examination revealed the patient to be thin but otherwise normal. Routine laboratory findings were normal, other than for occasional red and white blood cells in the urine. Blood total cholesterol was 260 mg. % with 72% esters, and bromsulphalein test showed 5% retention before treatment. Neither was repeated.

At time of discharge this patient had gained 1 pound and weighed 116 pounds. He has continued with the diet and insulin as at time of discharge to date (12 months).

DISCUSSION

Cases 1 and *2* illustrate the well-known effect of liver disease in aggravating the diabetic syndrome. In these patients combined medical and surgical treatment (high carbohydrate therapy and removal of infected gall bladders) resulted in dramatic improvements in carbohydrate tolerance.

Our results in *cases* 3 to 8, in which only mild or no liver dysfunction could be found by laboratory methods, also demonstrated very significant clinical improvement on intensive carbohydrate therapy. This suggests that the previous losses of carbohydrate tolerance in these patients were due to sub-clinical liver disease. At any rate it is difficult to conceive of any other simple basis for the favorable results which we observed.

It is possible, of course, that the mild liver dysfunction in 4 of the 6 non-surgical cases was coincidental, and did not determine the success of the treatment. If this were so, it would suggest a much wider field of usefulness for the treatment than was originally contemplated. Further tests on a larger series of cases will be necessary to settle this point. However, even if the therapeutic procedure is applicable only in cases of manifest or suspected liver disease, it probably merits wider application than might appear at first glance. It has recently been shown that many presumably normal individuals in the age group at which diabetes is most prevalent suffer from mild liver disease (6). It seems likely that diabetic patients would have a similarly high incidence of unsuspected liver disease.

The long standing belief that high carbohydrate intake without insulin may be harmful to the diabetic organism has been reaffirmed recently on the basis of changes in insulin content of the pancreas in animals (7), and denied on the basis of extremely high carbohydrate intake in diabetic patients observed under controlled conditions (8). Our treatment is not comparable to either of the above procedures in that we administered large amounts of insulin with the carbohydrate. The one patient in our series who did not benefit from the treatment certainly showed no evidence of any harmful effects therefrom.

Finally, there is the possibility that our favorable therapeutic results might have been due to the sodium chloride given during our intravenous injections rather than to the sugar itself. This seems most unlikely, in view of the patient who responded to oral treatment which was not accompanied by salt intake and in the light of the recent work of Strouse et al. (9).

SUMMARY

Two diabetic patients who developed cholecystitis with liver damage were observed before and after surgical treatment combined with high carbohydrate therapy aimed at treatment of the liver damage. The dramatic improvement in carbohydrate tolerance which occurred in these patients following treatment directed attention to another group of diabetic patients who were exhibiting unexplained losses in carbohydrate tolerance.

Of 6 diabetic patients with no overt clinical signs or symptoms of liver disease but with unexplained losses in carbohydrate tolerance, 4 yielded some laboratory evidence of liver dysfunction while 2 did not. All were treated as liver disease with intensive carbohydrate therapy plus insulin. With one exception these patients showed significant improvement in carbohydrate tolerance.

REFERENCES

1. Soskin, S.: The Liver and Carbohydrate Metabolism. *Endocrinology* 26: 297–308. 1940.
2. Soskin, S., and M. Hyman: Physiologic Basis of Intravenous Dextrose Therapy for Diseases of the Liver. *Arch. In . Med.* 64: 1265–70, 1939.
3. Soskin, S.: The Blood Sugar: Its Origin, Regulation and Utilization. *Physiol. Rev.* 21: 140–93. 1941.
4. Quick, A. J.: Intravenous Modification of the Hippuric Acid Test for Liver Function. *Am. J. Digest. Dis.* 6: 716–7. 1939.
5. Rosenberg, D. H., and S. Soskin: Comparison of the Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function. *Am. J. Digest. Dis.* In press.
6. Rosenberg, D. H.: The Cephalin-Cholesterol Flocculation Test in Liver Disease with Special Reference to the Diagnosis of Mild and Unsuspected Forms. *Arch. Surg.* In press.
7. Haist, R. E., J. Campbell and C. H. Best: The Prevention of Diabetes. *New England J. Med.* 223: 607–15. 1940.
8. Mirsky, I. A., A. N. Franzblau, N. Nelson and W. E. Nelson: The Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Coma. *J. Clin. Endocrinology* 1: 307–13. 1941.
9. Strouse, S., F. Buel R. Kay and D. Drury: Sodium and Potassium Salts in the Treatment of Experimental Diabetes and Diabetes Mellitus. *J. Nu ri ion* 21: 599–608. 1941.

Thyroid Globulin in the Treatment of Menstrual Irregularities

[Menstrual Disorders]

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IN A PREVIOUS ARTICLE entitled, "Thyroid in the Treatment of Menstrual Irregularities," the following statement appeared: "Each patient has been treated with desiccated thyroid in varying doses, an attempt having been made to raise the B.M.R. to zero or above, although in many cases this was not accomplished because of undesirable subjective symptoms" (1). Shortly after the above statement was made thyroid globulin became available. Experimental work on rats had shown that this preparation had less of an effect on the heart rate than the commercial thyroid powder (2). It seemed worth while to try this new substance on a few individuals to determine first, whether it was effective in the treatment of menstrual irregularities and second, if its use would eliminate the unpleasant symptoms such as nervousness and palpitation found so disagreeable to a few patients receiving desiccated thyroid. It is the purpose of this communication to report our experience in the use of thyroid globulin.

Twenty-eight patients were observed for a period of at least one year. Their ages ranged from 18 to 23 years with an average of 18 ½ years and the B.M.R. varied from −2 to −22%, the average being −10% (Wisconsin Standards used) (3). Cholesterol determinations and electrocardiograms were normal. Each patient was given thyroid globulin in a dose sufficient to result in either a normal B.M.R. or relief of the menstrual difficulties.

The results of therapy in this series are summarized in table 1 together with those in a similar group previously reported who received desiccated thyroid (1). Although the present group is too small for accurate comparison, it would seem that the two preparations are equally efficacious in this type of case.

TABLE 1. COMPARISON OF RESULTS OBTAINED WITH USE OF DESICCATED THYROID AND THYROID GLOBULIN IN TREATMENT OF MENSTRUAL IRREGULARITIES

Complaint	Total Cases		Complete Relief		Partial Relief		No Relief	
	Desiccated thyroid	Thyroid globulin	Desiccated thyroid	Thyroid globulin	Desiccated thyroid	Thyroid globulin	Desiccated thyroid	Thyroid globulin
Dysmenorrhea	25	20	17	11	5	6	3	3
Metrorrhagia	13	2	12	2			1	
Oligomenorrhea	17	9	17	5		3		1
Amenorrhea	4	1	1				3	1

Among the 28 patients receiving thyroid globulin, 13 had received desiccated thyroid previously with partial or complete relief of their symptoms. Six of this latter group noted no change with the new preparation. One preferred the desiccated thyroid. The remaining 6 had not tolerated the desiccated thyroid well because of nervousness and palpitation, which they considered more disagreeable than their menstrual irregularities. These 6 tolerated thyroid globulin without undesirable symptoms and with relief from their menstrual difficulties comparable to that with the desiccated thyroid. All patients who had poor results with the use of thyroid globulin were given a therapeutic trial with desiccated thyroid but there was no improvement with the latter preparation.

A brief résumé of the cases of two patients who tolerated the thyroid globulin in contrast to the desiccated thyroid follows.

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CASE REPORTS

M.C. (*101601*), an 18-year-old freshman, consulted the Student Health Department at the University of Wisconsin in Sept. 1938 because of severe dysmenorrhea. The onset of her menstrual periods occurred at 12 years. They had been regular each month, lasting 4 days, with a normal flow. Since the onset there had been severe backache and cramp-like pain in the lower abdomen lasting the first 2 days of the period and necessitating bed rest. The physical examination revealed no abnormalities. The height was 62¼ inches, the weight 126 pounds. Pelvic examination findings were normal. The B.M.R. was −3%. Desiccated thyroid, ½ grain daily, gave complete relief from the dysmenorrhea but resulted in nervousness with palpitation. The B.M.R. was then +4%. In June 1939 the medication was voluntarily stopped but by Aug. 1939 the dysmenorrhea recurred. At this time the B.M.R. was −3%. Because of the nervousness with the desiccated thyroid, thyroid globulin, ½ grain daily, was started. There was no further nervousness or cardiac consciousness and the dysmenorrhea was completely relieved. The improvement has been maintained to the present (Aug. 1941).

E.H. (*96631*), a 17-year-old freshman, consulted the Student Health Department because of severe dysmenorrhea. The onset of her menstrual periods occurred at 14 years. They were regular every 30 days with a normal flow lasting 4 to 5 days. Just before the onset of each period there was pain in the lower abdomen. This was present during the first day, recurred the last day and occasionally persisted for the entire period. The physical examination findings were within normal limits. The blood pressure was 132/80, height 68 inches, weight 179 pounds. Pelvic examination revealed the uterus to be in 2nd degree retroversion. The B.M.R. was −7%. In Mar. 1939 desiccated thyroid, ½ grain daily, was started. Later the dose was increased to 1 grain daily. There was complete relief from the dysmenorrhea but nervousness was present. In Oct. 1939 the blood pressure was 160/100, pulse 96, and the nervousness was marked despite the fact that the B.M.R. was −13%. All thyroid medication was stopped with the loss of the subjective complaints. The blood pressure dropped to 112/78 but the dysmenorrhea recurred and became increasingly more severe. Therefore, thyroid globulin, 1 grain daily, was tried. The dysmenorrhea has been controlled with this dose since that time, there has been no further elevation of the blood pressure and no recurrence of the nervousness.

DISCUSSION

Although each patient in this group had a B.M.R. below zero, none had abnormal blood cholesterols, electrocardiograms or clinical evidence of hypothyroidism. Relatively small doses of thyroid were adequate to obtain the desired results. In this small series it would appear that thyroid globulin and desiccated thyroid had comparable effects on the menstrual period. However, in a group similar to this, there are certain disadvantages in the use of thyroid globulin. First, with the relatively small dose used it was impossible to estimate clinically whether the B.M.R. had changed. There was no perceptible effect on the pulse rate, no tremor developed and the patient had no subjective symptoms as a guide. The B.M.R. was essential to determine necessary changes in the dosage. A second disadvantage was excessive perspiration and a sensation of warmth observed by 4 patients during the first few weeks while taking the thyroid globulin. These symptoms gradually became less, finally disappearing despite the continuation of the medication.

Occasionally, there is a patient who objects to desiccated thyroid because of the undesirable symptoms caused by its use, but at the same time the patient has complete relief from her menstrual difficulties when using it. Previously we have used mild sedatives together with the desiccated thyroid in these individuals but in our limited experience these patients tolerate thyroid globulin satisfactorily, thereby obviating the necessity of giving two drugs. However, after using the thyroid globulin for a period of 18 months, we have returned to the use of desiccated thyroid in all but this latter group, chiefly because it is much more satisfactory to follow patients clinically while receiving desiccated thyroid.

SUMMARY

Twenty-eight patients with B.M.R. ranging from −2 to −22% were given thyroid globulin because of menstrual irregularities. The results of therapy were comparable to a similar group who received desiccated thyroid. However, 6 individuals found the latter preparation disagreeable because of nervousness and palpitation. These patients tolerated the thyroid globulin without undesirable symptoms.

The thyroid globulin used was made available through the courtesy of Dr. A. E. Meyer of the Maltine Co., New York City.

REFERENCES

1. Foster, R. C., and M. J. Thornton: *Endocrinology* 24: 383. 1939.
2. Meyer, A. E., and M. Yost: *Endocrinology* 24: 806. 1939.
3. Stark, M. E.: *Am. J. Physiol.* 3: 630. 1935.

Treatment of Recurrent and Threatened Abortion

Report of Two Hundred and Twenty-six Cases

[Miscarriage]

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BECAUSE IT IS KNOWN to be physiologically essential in the inception and maintenance of pregnancy, the corpus luteum hormone has assumed a rôle of considerable importance in the treatment of conditions which threaten the premature termination of pregnancy, that is, habitual and threatened abortions. The purpose of this paper is to evaluate the use of progesterone in such cases.

Fraenkel (1) in 1903 demonstrated that the removal of the corpus luteum in a rabbit shortly after fertilization causes failure of implantation of the embryo, or if the embryo is already implanted, leads to abortion. The findings were confirmed and extended in studies which led to the isolation of the corpus luteum hormone, progesterone. In 1929 Corner and Allen (2) reported that they had been able to maintain pregnancy in ovariectomized animals by the administration of the corpus luteum extract. Other workers since have amply demonstrated that the maintenance of pregnancy is essentially an endocrine phenomenon, dependent upon adequate production of progesterone. In the early weeks this is supplied by the corpus luteum of pregnancy whose normal function is dependent upon adequate stimulation by gonadotropic hormone. Later, at the end of the second month or the beginning of the third month of gestation the production of progesterone is taken over by the placenta. This period of transition is the critical period at which time abortion is most likely to occur. The fact that the removal of the corpus luteum after the third month does not always result in abortion has led to the supposition that progesterone is unnecessary. This supposition is no longer tenable for progesterone seems to be necessary for the maintenance of pregnancy throughout its duration (3).

The physiological properties of progesterone which seem to be of most importance in the establishment and maintenance of pregnancy are the ability to produce and maintain the secretory differentiation of the endometrium and its depressant action on the myometrium.

The actual cause of spontaneous abortions when the factors of trauma and uterine pathology have been ruled out is a moot question. The theory has been held that abortion is nature's way of getting rid of an abnormal embryo. The studies of Mall, Huntington, Streeter, and Hertiz in the laboratory of Irving (4) are summarized by the latter, who reports that the examination of specimens revealed that 70% of abortions are due to developmental defects, 52% being defects of the ovum and 18% defects of its appendages, the placenta, membranes and umbilical cord. Of the 30% remaining, 17% were attributed to maternal defects, so that only 13% might have been prevented.

The deviation from the normal in the ratio of excretion of the chorionic gonadotropin, estrogens and pregnandiol in cases of threatened and habitual abortions would seem to indicate that there is a faulty endocrine mechanism with a relative progesterone deficiency in some of these cases (3). There is a marked fall in the production and excretion of the chorionic gonadotropic substance in most instances of abortion. This is probably not the cause of the abortion but rather the result of the degeneration of the chorion, the source of the hormone. The estimation of pregnandiol in such cases shows a decrease in excretion rate which would seem to indicate a progesterone deficiency due either to corpus luteum failure or failure of the placenta to take over the function.

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Some abnormality of hormonal secretion is the fundamental cause of two-thirds of the cases of spontaneous abortions according to Taussig (5). Such endocrine pathology may be one of three types: *a*) preconceptional conditions which influence adversely hyper-irritability of the uterine muscles due directly or indirectly to improper balance of endocrine secretions. It would appear, therefore, that some at least of the developmental abnormalities encountered in the products of abortions may be traced to faulty

TABLE 1. CASE REPORTS OF HABITUAL AND THREATENED ABORTION

Author	No. of Cases					Preparation Used	Method and Dosage	Remarks
	Total	Habitual	Threat.	Term	Aborted			
Hirst (10) 1918	3	3		2	1	Fresh ext. of dried C. L. 1 cc.=2 mg.	1 cc. 3×week, 2 and 3 mo. total 32–36 cc.	grav. 6, para. 0 grav. 5, para. 0 grav. 4, para. 0
Da Re (11) 1933	3	2	1	3	0	C. L. ext., 1 I.U.	1 cc. 3×wk. 1st 7 mo.	grav. 3, para. 0 grav. 2, para. 0
Shea (12) 1933	1	1		1	0	C. L. ext.	1 cc. 3×wk. 1st 38 wk.	grav. 3, para. 0 threatened 1st 3 mo.
Carmichael, Reynolds (13) 1934	1	1		1	0	Progesterone	1 I.U. at times threatened and 2–3 wk. thereafter for 6 mos.	grav. 3, para. 0
Portman (14) 1934	2	2		2	0	C. L. ext.	½ I.U., q. 1–2 dy.	
Hall (15) 1934	1	1		1	0	Progesterone	1/25 I.U. 1×wk., 7–16 wk.; 10 I.U. q. 3–5 days when threatened	grav. 5, para. 0 nausea and cramps
Saidl (16) 1934	3	3		3	0	C. L. ext.	½ I.U. daily when threatened, total 5–12 I.U. to 4 mo.	1 case of placenta praevia
Smith, (17) Johnstone 1935	2	2		0	0	C. L. ext.	1 I.U. 3×wk. until 4 mo.; thereafter 2 I.U. 3×wk. at time of period	2 cases grav. 2, para. 0
Rodecurt (18) 1936	3	3		3	0	Progesterone	Not given	3 sterility cases symptoms free
Asjes (19) 1937	1	1		1	0	Progesterone	1 I.U. 3×wk. for 1st 7 wk. Total=21 I.U.	grav. 4, para. 0
Clauberg (20) 1937	2	2		2	0	Progesterone	2–10 mg. q. 2–4 day beginning 2–4 days before critical pd. continuing 8–14 days.	
Vermelin (21) 1940	2	2		2	0	Progesterone		
Total	24	23	1	21	1			

the development of the sex cells in which instance the fertilized ovum does not develop beyond the stage of a primitive mass; *b*) developmental factors which influence implantation and nutrition of the ovum in the first trimester of pregnancy, and are dependent largely upon the proper functioning of the corpus luteum of pregnancy; and *c*) the condition of endocrine factors which lead to failure of development and eventual death of the embryo.

The rôle of nutritional factors in human abortions is an unknown quantity. Animal experimentation indicates that an important rôle is played by the vitamins. Vitamin C deficiency in guinea pigs leads to abortions in 50% of cases as reported by Vogt (6).

TABLE 2. SERIES OF CASES OF HABITUAL ABORTION

Author	No. of Cases				Preparation Used	Method and Dosage	Supplementary Therapy	Remarks
	Total	Threat.	Term	Aborted				
Antechi (22) 1928	21		19	2	C. L. ext.	1–2 cc. 2×wk. 1st. ½ pregnancy		
Wolfsohn (23) 1932	10		7	3	C. L. ext.	1 cc. q. 2 days 1st ½ pregnancy		1 failure, myoma; 1 failure hydratid mole
Kane (24) 1935	26		22	4	C. L. ext.	2 cc. q. other day for 10 doses repeated q. 3 wk.	thyroid, NaI, no intercourse	3 abnormal babies, spina bifida; pyloric stenosis; mongolian
Kane (24) 1936	14		14	0	Progesterone	1/25 R.U. as above	As above	
Krohn, Lackner, Falls (25) 1935–1936	30	17	24	6	C. L. ext., 1 cc.=1 I.U.	1 unit 2 wk. until 32nd wk.		
Bishop (26) 1937	22		15	7	Progesterone	2–8 mg. weekly beginning 5–9 wks. and continued to 16–30 wks.	vit. E	
Gershenfeld(27) 1937	27		20	7	Progesterone	1 I.U. wk., 2–3 I.U. at time of period. 1–2 I.U. dy. for bleeding	vit. E	
Elden (28) 1938	8	5	6	2	Progesterone	1 I.U. weekly until 6 mos., total 10–44 mg.	none	Baby cyanotic at birth, normal at 6 wks. 1 abortion due to previous operation
MacGregor (29) Stewart 1939	22		14	8	Progesterone	1 mg. 2× wk.; occasionally increased to 3–5 or 10–20 mg. 2×wk.		Failure attributed to low dosage, of 1 mg. 2×wk.
Campbell (30) Sevringhaus 1940	13		4	2	Progesterone	1–2 I.U. per week, started immediately and continued 24–26 wks.		
Huber (31) 1940	15		14	1	Progesterone	1 I.U. weekly, 2 I.U. weekly at time of missed period		
Mazer, Israel (32 1940	35	22	28	7	Progesterone	1–5 I.U. 2×wk. until quickening; 1–5 I.U. daily for bleeding	vit. E. thyroid	15 first seen when spotting, all went to term; 20 treated prophylactically; 7 aborted; 1 still birth; 1 absent hand
Krohn (33) Harris 1941	11	6	10	1	Progesterone (orally)	10 mg. 2×wk. until quickening; 10 mg. daily at time missed period; threatened, 1–10, 2×day	6 mg. pregnenin-olone=1 mg. progesterone	
Collins (34) 1940	7	6	4	3	Progesterone	1 I.U. when symptoms occur	wheat germ oil, thyroid, chlorionic gonadotropic hormone	1 abortion due to malaria; 1 missed abortion
Tholen (35) Stolte 1939	12		8	4	Progesterone	2 I.U. daily for bleeding	Salt free diet, thyroid vit. E	
Total	273	56	216	57				

Ley (7) gave vitamin C to 10 women who habitually aborted, with only one failure. It is said that vitamin C stimulates the growth of the corpus luteum. Both authors emphasize the fact that the corpus luteum contains large quantities of vitamin C. Vitamin E deficiency (9) causes degenerative changes in the placenta in rats with ultimate abortion or stillbirth of the fetus. Many authors are reporting good results from the use of vitamin E in the treatment of habitual and threatened abortions in the human. Its method of action is unknown and its therapeutic efficacy unproven in the human.

There are at least three factors, probably also interactive, which may be causative agents in abortions, namely, defective germ plasm, endocrine and nutritional deficiencies. In the first no amount of therapy will affect the outcome of the pregnancy. The second and third may be amenable to treatment. The problem is to recognize these cases as such and treat them adequately.

Based on the theory that many cases of habitual and threatened abortion are due to progesterone deficiency, clinical reports of its use in such cases have appeared since 1932 when progesterone first became available. Representative reports may be divided into three groups. *Group 1* consists of case reports in which progesterone was used prophylactically in habitual abortions. *Group 2* reports series of more than 10 cases similar to those of *Group 1*. *Group 3* consists of series of cases in which progesterone was used as active therapy in cases of threatened abortion.

In *Group 1* (table 1) there was a total of 24 cases which were treated with progesterone; 23 of these were of habitual abortion and 22 went to term. One case of threatened abortion also went to term. There is only one failure reported, giving about 96% success. The report of Hirst (10) in 1918 is included because he is apparently the first to have used this form of therapy with success. It is questionable whether the results in a single case have a great deal of significance. However, since these cases represent women who had had multiple spontaneous abortions, the good results seem to be encouraging. MacGregor and Stewart (29) have estimated that statistically a woman who has aborted twice has only a 50% chance of having a successful pregnancy while those who have aborted 3 and 4 times have only a 20% and 10% chance respectively. The probabilities, therefore, are that at least some of these women would have aborted without therapy. The dosage used varied but on the average 1 I.U. was given twice a week through 3 months of pregnancy.

TABLE 3. SERIES OF CASES OF THREATENED ABORTION

Author	No. of Cases			Preparation	Method	Supplementary
	Total	Term	Aborted			
Collins (34) 1940	16	13	3	Progesterone	1 I.U. daily, until symptoms subsided	Wheat germ oil; chorionic gonadotropin; thyroid
Krohn, Lackner (25) Falls 1935–1936	11	10	1	Corpus luteum extract	1 I.U. 2×day until symptoms subsided	
Krohn, Harris (33) 1941	39	32	7	Progesterone	10 mg. 2×day until symptoms subside; thereafter 10 mg. 2×week	
Feiman (36) 1939	3	2	1	Progesterone	2 mg. daily until symptoms subside and 2 mg. per wk. for duration of preg.	
Total	69	57	12			

In series of cases treated with progesterone for habitual abortion (table 2) the percentage of success fell to 79%. Of the 273 cases reported by 12 authors 216 went to term and 57 aborted. The dosage seems to be somewhat higher than was used in the preceding group. Whether supplementary therapy such as thyroid and vitamin E was used is not always stated but it was used in several instances. Campbell and Sevringhaus (30) report success in 11 of 13 cases in which only progesterone was used.

The use of progesterone in threatened abortion has probably been extensive but few reports have appeared in the literature, probably because the results have been rather disappointing. Reports by 4 authors of 69 cases give an 81% success (table 3).

Classification of Cases and Method of Treatment

This report deals with 226 cases in which pregnancy seemed to be jeopardized, either on the basis of a history of recurrent abortion or sterility, or by

the occurrence of bleeding. These cases may be classified as follows.

A. *Recurrent Abortion or Sterility* (42 cases)

1. Progesterone used prophylactically in 42 cases
   - *a.* Went to term, 33
     - No bleeding, 33
     - Bleeding, 0
   - *b.* Premature, 4
     - No bleeding, 0
     - Bleeding, 4
   - *c.* Aborted, 5

B. *Threatened Abortion* (184)

1. Progesterone used in 139 cases
   - *a.* Went to term, 64
     - One episode of bleeding, 47
     - Multiple episodes of bleeding, 17
   - *b.* Premature, 10
     - One episode of bleeding, 7
     - Multiple episodes of bleeding, 3
   - *c.* Aborted, 65
     - One episode of bleeding, 52
     - Multiple episodes of bleeding, 13

2. Progesterone not used, 45
   - *a.* Went to term, 22
     - One episode of bleeding, 18
     - Multiple episodes of bleeding, 4
   - *b.* Premature, 6
     - One episode of bleeding, 5
     - Multiple episodes of bleeding, 1
   - *c.* Aborted, 17
     - One episode of bleeding, 13
     - Multiple episodes of bleeding, 4

In the group of 42 cases which received progesterone prophylactically, 36 gave a history of one or more previous unsuccessful pregnancies, while 6 cases had been treated for primary sterility. It has been our experience that patients who have overcome a primary sterility of endocrine origin have an increased tendency to abort and we therefore treat them similarly to the cases of habitual abortion.

Besides the routine physical examinations, blood counts and urinalysis, all of these patients had basal metabolic rate determinations and Kahn tests. The physical and pelvic findings were normal in all cases. The B.M.R. was variable, and the Kahn tests negative in all. In addition, the 6 primary sterility patients had complete endocrine studies including estrogen determinations of the blood and urine, endometrial biopsies and pregnandiol determinations of the urine.

All of the patients in this group received injections of progesterone, usually 1 mg. twice weekly. A few in the latter part of the series received 5 mg. twice a week. Injections were begun as soon as the diagnosis of pregnancy was made and continued through the third to fifth month. In addition, all received vitamin E, either natural or synthetic. Almost all received thyroid by mouth in doses varying with the B.M.R. In all of these cases the adjuncts of rest, restriction of intercourse, limitation of exercise, and elimination of the use of enemas and strong laxatives were used.

The 9 cases which bled had additional therapy for the threatened abortion. This usually consisted of progesterone, 1 to 5 mg. once or twice daily during the period of bleeding, bed rest, and increased doses of vitamin E.

In the threatened abortion group are included all cases which had one or more episodes of bleeding during the first 8 months of pregnancy and which had not received progesterone prophylactically. No attempt has been made to differentiate the inevitable abortions from the threatened abortions. In none of these cases was there any general or pelvic condition which would have made abortion inevitable, although minor pathological conditions as small fibroids and retroversion were occasionally present.

There were 184 cases of threatened abortion of which 139 received progesterone and 45 did not. The dosage of progesterone varied with the amount and duration of the bleeding. Most of the patients in the early part of the series received 1 mg. once or twice a day, while in the latter part of the series this was increased to 5 mg. 2 to 3 times a day. In addition most of these patients received thyroid and vitamin E, either in the form of wheat germ oil, 2 capsules 3 times a day, or alpha tocopherol, 3 mg. three times a day. Those patients who received no progesterone therapy fall into 2 categories, first, those in which the bleeding was so slight in amount and short in duration that treatment was not considered warranted, and second, those patients who were seen so late that treatment was considered useless. All patients who had bleeding for more than 2 days and many whose bleeding was of shorter duration were hospitalized. In the remainder bed rest was ordered until the bleeding had subsided.

RESULTS

Prophylactic Therapy

The results obtained in the prophylactic group together with their obstetrical histories are summarized in table 4. In the 6 patients who had been primary sterility problems, 1 had bleeding during the course of her pregnancy but went to near term and gave birth to a viable premature infant. The other 5 cases all resulted in normal full term infants with no evidence of abnormality.

In the 36 patients who had had previous unsuccessful pregnancies there had been a total of 72 pregnancies terminating in 8 full term infants, 6 stillbirths, 57 abortions and one ectopic pregnancy. Nineteen of these patients had had only 1 pregnancy, none of which terminated with a viable child. In the 17 cases which had had more than 1 previous pregnancy, one or more of which terminated in abortion, there had been a total of 53 previous pregnancies with only 8 viable infants.

Under treatment, 28 of the 36 patients carried through to term without any evidence of bleeding. Three patients had some bleeding during the course of their pregnancies and 5 aborted. All 3 of the patients who had bleeding during the course of their pregnancies went into labor and were delivered 2 or more weeks prior to the expected dates of confinement.

Treating the group as a whole, there were 42 cases which received progesterone prophylactically. Of these, 5 aborted, 4 delivered premature but viable infants and 33 went to full term, which figures represent successful pregnancies in 88% of the cases. In the group having 1 previous pregnancy there were 19 cases which terminated in 4 abortions and 15 full term infants, which represents successful pregnancies in 79% of the cases. In the 17 cases of so-called habitual abortions in which there had been more than 1 previous unsuccessful pregnancy, 16 terminated in full term deliveries and only 1 in abortion. This represents 94.1% successful pregnancies. In the entire group of 42 patients there were no abnormal infants.

Threatened Abortion

Results and previous obstetrical histories. The results obtained with the 184 cases that bled during the first eight months of gestation and the previous obstetrical histories are summarized in table 5. One hundred and two (55.4%) of these patients carried through to delivery of viable infants while 82 (44.6%) aborted. Of the 102 patients who gave birth to viable babies there were 16 whose babies were 2 or more weeks premature according to the expected date of confinement.

The group consisted of 89 primiparae and 95 multiparae. Abortions occurred in 49.4% of the multiparae and 39.3% of the primiparae. In the group of multiparae who bled during this pregnancy there had been 148 previous pregnancies which had resulted in 83 full term infants, 7 prematures, 4 stillbirths and 54 abortions. Of the 47 multiparae who aborted this pregnancy, 23 had previous histories of obstetrical abnormalities.

Duration of bleeding and termination of pregnancy. The relation of the duration of bleeding to the ulti-

TABLE 4. PREVIOUS OBSTETRICAL HISTORIES OF CASES IN WHICH PROGESTERONE WAS USED PROPHYLACTICALLY, 42 CASES

Previous Pregnancies								Present Pregnancy		
								Term		Aborted
No. per case	No. of patients	Total pregnancies	Full term	Premature	Stillbirths	Abortions	Ectopics	Without bleeding	With bleeding	
0	6	0	0	0	0	0	0	5	1	0
1	19	19	0	0	3	16	0	14	1	4
2	9	18	4	0	0	14	0	8	1	0
3	5	15	3	0	0	11	1	3	1	1
4	2	8	1	0	1	6	0	2	0	0
12	1	12	0	0	2	10	0	1	0	0
Total	42	72	8	0	6	57	1	33	4	5

TABLE 5. PREVIOUS OBSTETRICAL HISTORIES OF CASES OF THREATENED ABORTION, 184 CASES

Previous Pregnancies						Present Pregnancy		
No. per case	Total cases	Full term	Stillbirths	Premature	Abortion	Term	Premature	Abortions
0	89	0	0	0	0	46	8	35
1	60	39	3	1	17	28	5	27
2	23	26	1	3	16	10	1	12
3	6	4	0	3	11	0	2	4
4	6	14	0	0	10	2	0	4
Total	184	83	4	7	54	86	16	82

mate termination of the pregnancy in those 142 patients having only one episode of bleeding is summarized in table 6. The group which bled for only 1 day is subdivided into those who only spotted and those in whom abortion was inevitable. Those classified as inevitable all passed the fetus or were subjected to curettage within 12 hours and, therefore, cannot be considered as treated cases. Ten of these cases received 1 dose of progesterone while 7 received none. All of the 45 cases who spotted for only 1 day went to term. Twenty-five received progesterone therapy and 20 did not.

TABLE 6. DURATION OF BLEEDING, ONE EPISODE

Duration of Bleeding	Total No. Cases	Progesterone Used		Progesterone Not Used	
		Term	Aborted	Term	Aborted
1 day					
Inevitable	17	0	10	0	7
Threatened	45	25	0	20	0
2–7 days	57	23	25	3	6
7–30 days	23	6	17	0	0
Total	142	54	52	23	13

TABLE 7. DOSAGE OF PROGESTERONE, ONE EPISODE OF BLEEDING

Dosage Mg.	Duration of Bleeding					
	1 Day		2–7 Days		8–30 Days	
	Term	Aborted	Term	Aborted	Term	Aborted
1	17	4	4	3	0	0
2– 5	3	4	10	13	0	5
6– 10	2	0	1	3	2	5
11– 20	1	2	3	2	1	3
21– 30	2	0	3	2	3	1
31– 40	0	0	0	2	0	0
41– 50	0	0	2	0	0	0
51–100	0	0	1	0	0	3
Total	25	10	23	25	6	17

In the patients who bled for more than 1 day, 71 received progesterone and 9 did not. Of those who received progesterone 42 (59.1%) aborted while 6 (66%) of those who did not receive progesterone aborted. If this is analyzed further, of the 57 patients who bled from 2 to 7 days, 31 (54.3%) aborted, while of the 23 cases who bled for more than one week 17 (73%) aborted.

Dosage of progesterone. The relationship of the duration of bleeding to the dosage of progesterone in the 106 cases which had only one episode of bleeding is illustrated in table 7. Fifty-four of these cases carried to term and 52 aborted. As might be expected, the total dosage corresponded roughly to the duration of the bleeding. The size of the dose was about equal in the group that carried to term and in those who aborted. Many of the cases in the group that carried to term continued to receive treatment after the episode of bleeding.

Multiple episodes of bleeding. There were 42 cases which had more than one episode of bleeding. The data is presented in table 8. Of these 25 carried to delivery of viable infants, 20 with progesterone and 5 without progesterone. In the 17 cases which aborted, 13 received progesterone at one or more of their periods of bleeding while 4 did not. In almost all of the cases which had more than 3 episodes of bleeding, there were some causes extraneous to the pregnancy for the bleeding.

TABLE 8. MULTIPLE EPISODES OF BLEEDING, 42 CASES

No. Episodes of Bleeding	Progesterone Used		Progesterone Not Used		Total
	Term	Aborted	Term	Aborted	
2	12[1]	4	4[3]	2	22
3	5[2]	6[4]	1	1	13
4	1	3	0	1	5
5	0	0	0	0	0
6	1[5]	0	0	0	1
7+	1[6]	0	0	0	1
Total	20	13	5	4	42

[1] Two patients had eroded cervix.
[2] Two patients had eroded cervix, one had fibroids.
[3] One anencephalic monster.
[4] One patient had ovarian cyst removed.
[5] Eroded cervix.
[6] Placenta praevia.

Time incidence of abortion. The relationship of the incidence of bleeding and abortion to the progress of gestation is illustrated in figure 1. The highest incidence of abortions occurred in the second and third months. Probably many more abortions occur during the first month than are indicated here but physicians

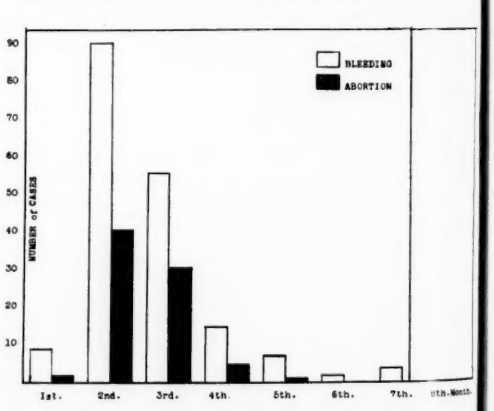

FIG. 1. TIME INCIDENCE OF BLEEDING AND ABORTION DURING THE MONTHS OF PREGNANCY

do not see such cases. Of the cases which bled during the first month, 22% aborted, in the second month 46.1%, in the third month 55.3%, in the fourth month 33.3% and in the fifth 14.2%. None of the cases in which bleeding first occurred in the last trimester of pregnancy failed to carry through to term. The bleeding coincided with the time of the missed period in 9 cases in the first month, 29 cases in the second month, 13 cases in the third month, and in 2 cases in the fourth month.

Incidence of fetal abnormalities. In the 102 cases of threatened abortion carried to delivery of viable infants there were 5 fetal abnormalities (4.9%), 3 occurring in the group which received progesterone (2.9%), and 2 in the group which did not (2%). The abnormalities of the group which received progesterone were hypospadias, dextrocardia, and a mongolian idiot. In the group which bled but received no progesterone there occurred one anencephalic monster and one thyroid cyst.

DISCUSSION

It has long been observed that those cases which become pregnant after the treatment of primary sterility of endocrine origin have a marked tendency to abort. Prophylactic treatment with progesterone in these 6 cases resulted in 5 full term infants, and one premature, all of whom survived. We have no comparable series in the literature to use as a basis of comparison, but we cannot help but feel that these results are better than those obtained in a similar group without treatment.

In the prophylactic treatment of those patients who had had one or more previous unsuccessful pregnancies, several facts stand out. First, the popular impression that each succeeding abortion reduces the chance of an eventual successful pregnancy is certainly not borne out by our figures if the case is adequately treated. It would seem that the patient with 3 or 4 previous abortions has just as good a chance with the succeeding pregnancy as the patient who has had only one abortion. It may be that each succeeding pregnancy alters the endocrine makeup of the individual, each of these slight changes bringing the patient more nearly into a normal balance, so that the patient who has had several abortions may have a slightly better chance for a successful pregnancy than the patient who has had only one. Our figures seem to indicate such a tendency.

Of the 42 cases in the combined prophylactic group (table 1), 4 bled during the course of their pregnancies but carried through to delivery of viable infants. All 4 of these patients were delivered spontaneously 2 or more weeks prior to the expected date of confinement. None of the other 33 cases in this group who delivered viable infants had any evidence of prematurity. This would seem to indicate that the same factors which were responsible for the bleeding in early pregnancy were also responsible for the onset of premature labor, and that the etiology of premature labor should be sought for in the endocrine makeup of the individual. For this reason we believe that progesterone should be continued to term in patients who bleed during the course of their pregnancies. By so doing it may be possible to inhibit the uterine musculature enough to allow these patients to carry through to term.

In view of the fact that the 17 multiparae, who had previously produced only 8 viable infants in 53 previous pregnancies were able to produce 16 viable infants out of 17 pregnancies under treatment, there seems to be little doubt as to the efficacy of this method of therapy in habitual abortions. *Case 1* illustrates the value of progesterone in habitual abortion.

Case 1. (Courtesy Dr. H. G. Hadley.) Mrs. M. C. para. 0, grav. 13, age 40. This patient had had 10 previous pregnancies varying from 1 to 5 months in duration, and 2 macerated fetuses, one at 7 and the other at 8 months. She was seen by us early in her 13th pregnancy. Her past history, other than her obstetrical history, was essentially negative. General physical examination was negative. Pelvic examination revealed normal external and internal genitalia. The Wassermann reaction was negative, and the B.M.R. was well within normal limits. The urine was negative for albumen and sugar. A fasting blood sugar was 84 mg. The blood count showed only a slight secondary anemia. She was placed on wheat germ oil (Abbott), capsules 2, *t.i.d.*, thyroid gr. $\overline{SS}$ *t.i.d.*, and progesterone, 1 mg. twice a week. Her pregnancy was entirely uneventful, but in view of the previous history of fetal deaths, she was delivered by caesarean section of a normal female infant weighing 5 pounds 8 ounces about 2 weeks before the expected data of confinement. She made an uneventful recovery. Following this episode, she again became pregnant, and returned to her family physician, who put her on the same regime. Unfortunately she no longer felt that she needed intensive treatment and was very negligent about getting her injections of progesterone, although she took the thyroid and the wheat germ oil. She aborted in the third month of her pregnancy.

The results obtained in the treatment of threatened abortion are not nearly so successful as those of cases treated prophylactically. Many factors enter into the unsuccessful termination of a pregnancy over most of which we have little control. These include faulty germ plasm, pelvic pathology and systemic disease. Mott (37) claims that 12% of all abortions are the result of a faulty germ plasm which produces fetal abnormalities that are incompatible with life. The incidence of fetal abnormalities in spontaneous abortions is placed as high as 70% (4). These fetuses are doomed to die in utero and fortunately no amount of therapy will carry them to term. Anatomical ab-

normalities such as faulty implantation, small submucous fibroids, retroverted and incarcerated uterus may also result in unavoidable abortions. Systemic diseases may occasionally result in abortion but we have been fortunate in having few such cases in this series. There have been no cases of the usual systemic diseases such as severe nephritis, diabetes, heart disease and only one of syphilis which was under active therapy throughout the pregnancy and went to term. There was one case of systemic disease which, while still a matter of some controversy, seems worthy of mention.

Case 2. Mrs. C. C., age 27, para 0, grav. 2, L.M.P. Sept. 5, 1939. Patient began to bleed on Oct. 18, 1939, and was treated by bed rest, progesterone, vitamin E, and thyroid. The bleeding stopped but recurred on Nov 12, and she aborted on Nov. 14. On Jan. 1, 1940, the patient had acute fever accompanied by muscular pains, headaches, chills and general malaise. She gave a history of similar previous attacks occurring over a period of four years. Agglutination tests for *B. abortus* were positive in 1:80 dilution. The brucellergin skin test was strongly positive. We believe this to be a true case of habitual abortion due to *Brucellus abortus* infection.

Many of the cases which we have listed as threatened abortions are really inevitable inasmuch as the fetus has expired and the placenta has separated from its attachment before symptoms appear. Clinically, the cases are indistinguishable from the truly threatened abortions. No amount of treatment will benefit these cases. On the other hand, large doses of progesterone may so inhibit the uterine musculature that these inevitable abortions become delayed or retained abortions. Occasionally these retained elements may degenerate and be expelled as a foul necrotic discharge. The following report illustrates such a case.

Case 3. Mrs. M. L., para. 1, grav. 3, L.M.P. Dec. 12, 1938. Some bleeding occurred Feb. 27 at which time a diagnosis of pregnancy was made. She was given 1 mg. of progesterone on Mar. 2, 6, 11, 13 and 22. On Mar. 1 she started to bleed slightly and ceased Mar. 13. On Mar. 2, a Friedman test was positive but on Mar. 24, a repeat Friedman was negative. A curettage was done but very little tissue could be found in the uterus. The pathologist's diagnosis was "endometrial hyperplasia, lutein phase." Subsequently this patient had a uterine suspension and then a normal pregnancy without progesterone therapy.

To avoid treating a patient as a case of threatened abortion when the fetus is no longer viable, a Friedman test should be done if the patient has been bleeding for 7 days or more. If the test is positive a careful pelvic examination and inspection of the cervix should be made to rule out extraneous foci of bleeding. Unfortunately, the Friedman test does not become negative for several weeks after the fetus has expired so that it may be necessary to repeat the test at intervals until a negative result is obtained. The importance of this procedure is well illustrated by the following case.

Case 4. Mrs. M. H., was first seen Mar. 16, 1940, She had been bleeding continually since Jan. 1, 1940, a period of 3½ months. On pelvic examination the uterus was enlarged and soft. Speculum examination revealed a marked bloody discharge coming from a perfectly normal cervical os. A diagnosis of missed abortion was made and a curettage performed Mar. 27, 1940. A perfectly normal viable fetus of 3½ months was removed from the uterus.

The question arises as to whether patients who have had only one previous abortion should be treated prophylactically. It has been held that a woman should not be considered as an habitual aborter until she has had at least two spontaneous miscarriages. Our data does not substantiate this. Most of the multiparae who bled had definitely abnormal obstetrical backgrounds (table 5). The fact that bleeding occurred in the present pregnancy would seem to indicate that they are on their way to becoming habitual aborters. We feel that those patients who have had abortions, miscarriages and stillbirths in their previous pregnancies should be treated prophylactically even though they have had a successful pregnancy at the last attempt. An intervening successful pregnancy does not appear to increase the chances of a successful outcome.

The data presented in figure 1 clearly demonstrates that the danger of abortion seems to reach its peak at the end of the second month and the beginning of the third month. This is the time at which the corpus luteum function begins to wane and the placenta takes over the function of producing progesterone. In this series of 184 cases, 91 cases or 49.4% had their first or only episode of bleeding in the second month of which 42 or 46.1% aborted. About one-third of these episodes represented bleeding at the time of the expected period. In the third month there were 56 cases or 30.4%, 31 or 55.3% of which aborted. There are probably more abortions in the first month of pregnancy that do not come for medical care. This data very clearly demonstrates that if progesterone is to be given prophylactically it should be started early, certainly in the first month, continued through the third month at least, and increased dosage with other precautionary measures taken at the expected time of the second, third and fourth missed periods. The figures show, however, that the danger of abortion does not disappear after the third month in spite of the fact that the placenta takes over the function of producing progesterone at this time. The hormonal imbalance persists in a few cases and these cases are benefited by the continued use of progesterone. Sterility patients, habitual abortion cases and those who have bled during the pregnancy should

have prophylactic treatment continued at least until the end of the fifth month and preferably to term.

Furthermore, of the 102 cases which bled and went to term (table 5), 16, or 15%, resulted in premature birth. In most of these cases treatment was discontinued after the episode of bleeding was passed. Again, the correlation between the incidence of bleeding during pregnancy and of prematurity seems to be obvious.

The data summarized in table 6 indicates rather clearly that the gravity of the prognosis increases with the duration of the bleeding. In the group which spotted for 1 day only, all of the patients went to term whether treated or not. In those who bled 2 to 7 days, 54.3% aborted while of those who bled more than 7 days, 73% aborted. Analysis of the individual cases which bled more than 7 days reveals that most of these patients had retained a dead fetus or more commonly were bleeding from other than the placental site. But prolonged bleeding is not always completely incompatible with life of the fetus as illustrated in *case* 4. It is not always easy to differentiate these conditions. A policy of watchful waiting with frequent repetition of pregnancy tests and occasional careful examinations to eliminate other foci of bleeding is the best course to follow in these cases.

The patients who bleed in the last trimester of pregnancy probably should not be classed as threatened miscarriages and probably should not be treated as such. Of the 15 cases which had bleeding continuing into the last trimester of pregnancy, none miscarried. Those patients who do miscarry during this period after an episode of bleeding do so as a result of premature separation of the placenta, placenta praevia or fetal death. Most of the cases listed probably come under the heading of slight premature separations of the placenta. Low implantation may also give recurrent episodes of bleeding before any gross hemorrhage leads to the establishment of the diagnosis.

Case 5. Mrs. E. M., para 0, grav. 1, L.M.P. May 13, 1940. E. D.C. Feb. 20, 1941. This patient bled at the time of every expected period for 8 months. She had previously been treated for sterility. She received 1 mg. of progesterone twice a day during every episode of bleeding. On Feb. 12, 1941, she had a profuse hemorrhage. X-ray of the uterus revealed the placenta was implanted low on the anterior wall encroaching on the internal os. A classical caesarean section was done and the patient delivered of a living male infant weighing 5 pounds, 2 ounces.

Analysis of the group of cases that had more than 1 episode of bleeding (table 8), brings out some interesting points. It was noted that bleeding frequently occurred at intervals of about 28 days. This verifies the accepted idea that bleeding and abortion are most likely to occur on or about the time of the expected period. Because of this fact, it may be wise to restrict activity and give larger and more frequent doses of progesterone to those patients who are receiving prophylactic treatment, and more especially in those cases which have had previous episodes of bleeding. This data also illustrates the fact that multiple episodes of bleeding do not seem to increase the chances of aborting. The incidence of abortion in those patients who had multiple episodes was no greater than the incidence in the group as a whole.

But multiple episodes of bleeding occurring at monthly intervals should be viewed with suspicion, especially if the patient is receiving large doses of progesterone. The injection of progesterone may so inhibit the normal cycle that only a bloody discharge may occur at the time of the normal cycle even though the pregnancy has been discharged some months previously. The following case is an illustration of this.

Case 6. Mrs. R. C., age 39, grav. 4, para. 1. First 2 pregnancies ended in spontaneous abortion. Received progesterone third pregnancy and went to term. L.M.P. Nov. 11, 1937, but was first seen during this pregnancy May 25, 1938. She bled May 17, and May 28–30, and was hospitalized May 31–June 7. Progesterone was given daily throughout the period of bleeding. Bleeding recurred July 27, Aug. 22–27. A dilatation and curettage for missed abortion was performed Aug. 28, 1937.

In order to avoid such a situation, Friedman tests should be performed after each episode of bleeding. Even this precaution does not always protect from error, as the following case illustrates.

Case 7. Mrs. M. K., para 0, grav. 1, seen first on Oct. 28, 1937. L.M.P. Sept. 10, 1937. At the time the patient was first seen she was having a dark bloody discharge. She was given progestin, 1 unit daily, and a Friedman test was done. It was positive. Progestin was cut down to twice a week and the bleeding ceased. She began to have a dark bloody discharge again Nov. 2, 1937, and again was given progestin daily. Another Friedman was done and was reported positive on Nov. 22, 1937. On Nov. 23, 1937, the bleeding became more profuse and a dilatation and curettage was done. Very little tissue could be found in the uterus. Pathologist reported "decidua and chorionic villi."

The dosage used in these cases has been entirely empirical as we do not know what the optimum dosage is. One fact seems obvious, that we have undertreated the patients rather than overtreated them. This is in rather startling contrast to the excellent results reported with very much smaller dosage. It has been our custom to administer as large doses as are consistent with the obvious limitations of private practice. We are sure that the larger doses now in use do no harm and may be more efficacious than the smaller dose previously administered. Brown, Henry and Venning (3) have demonstrated that the corpus

luteum of pregnancy produces 5 to 10 mg. of progesterone per day up to the 70th or 80th day of pregnancy and that in the fourth and fifth months the placenta produces 20 to 50 mg. per day. From these studies they conclude that doses less than 5 mg. daily, or every other day, are unlikely to have much effect. Such dosage should be increased in the presence of persisting symptoms and at the time of transfer of formation of progesterone from the ovary to the placenta.

Lists of dosage of progesterone in relation to the duration of bleeding in the groups who did and who did not carry through to term as listed in tables 7 and 8 illustrate the fact that in general the longer a patient bled the larger the total dosage of progesterone. There is no correlation between the size of the dose of progesterone and the incidence of abortion.

The question has often arisen as to whether in salvaging some of these pregnancies we may not be perpetuating errors which nature is doing her best to eliminate. Shute (38) who collected the data in the literature on fetuses delivered after threatened abortion successfully treated by either vitamin E and/or progesterone found that of 443 patients so treated 2% expelled deformed fetuses and he concluded that such therapy "may actually facilitate completion of inadequate development of certain types of defectives if given time."

It would seem from this data that abnormalities occurred rather frequently in that group of patients who bled during pregnancy but carried through to delivery of viable infants. Mott (37) gives the occurrence of fetal abnormalities as 0.6% in term pregnancies, while in our series of bleeding cases, they occurred in 4.9%. From the data, however, we cannot accuse progesterone of being responsible for the perpetuation of these defective pregnancies, as just as large a percentage carried through without the use of the hormone. However, occasionally a case occurs which makes us believe that such a possibility cannot be entirely disregarded.

Case 8. Mrs. L. J., para. 0, grav. 1, L.M.P., Jan. 28, 1940. E.D.C. Nov. 5, 1940. Patient began to bleed on Apr. 21, 1940. She stopped bleeding the next day but she was given a daily dose of progesterone for 3 more days. On June 14, 1940, she began to have severe uterine contractions occurring first every 5 minutes and later every 3 minutes. She was hospitalized and given 5 mg. of progesterone *t.i.d.* and morphine gr. ¼ P.R.N. After 3 days the contractions ceased and the patient was discharged. On Oct. 9, 1940, the patient was delivered of a mongolian idiot weighing 7 pounds, 5 ounces.

SUMMARY

In the series of 226 cases there were 42 cases with histories of recurrent abortion or primary sterility who received progesterone prophylactically and 184 cases of threatened abortion of which 139 received progesterone and 45 did not.

In the prophylactic group 33 went to term with no bleeding, 4 bled and were delivered prematurely and 5 aborted. In the group of threatened abortions 64 went to term, 10 were premature and 65 aborted under progesterone therapy. Of those which received no progesterone, 22 went to term, 6 were premature and 17 aborted.

The dosage of progesterone used varied but on the average it was given in 1 mg. doses twice a week for the first 3 months in the prophylactic group, and 1 to 5 mg. once or twice a day until symptoms subsided in the cases of threatened abortion.

The highest incidence of bleeding in the cases of threatened abortion occurred in the second month (49.4%) of which 46.1% aborted. One-third of these episodes represented bleeding at the time of the expected period. The second highest incidence of bleeding occurred in the third month (30.4%), but the percentage of abortion (55.3%) was higher than in the second month.

Of the 184 cases which were threatened abortion, all of the 45 patients which bled for only 1 day went to term whether they received progesterone or not. Of those who bled 2 to 7 days 53.5% aborted while of those who bled more than 7 days, 73% aborted.

Of the 102 cases which had 1 episode of bleeding but went to term, 16 (15%) resulted in premature births.

There were 5 fetal abnormalities (4.9%) in the cases of threatened abortion which went to term. There were 3 abnormalities in the group which received progesterone, namely, hypospadias, dextrocardia, and mongolian idiot; and 2 in the group which received no progesterone, an anencephalic monster and a thyroid cyst.

CONCLUSIONS

Progesterone is of definite value in the treatment of recurrent abortion. Theoretically, it would be desirable to study progesterone by means of pregnandiol determinations as a basis for selection of cases for progesterone therapy. Unfortunately, at the present date this is impractical. Therefore, to be on the safe side, cases which have had previous spontaneous abortions should be considered as potential aborters in the current pregnancy and treated accordingly. Progesterone to be effective should be started early and continued regularly through the fifth month of pregnancy with added precautionary measures at the time of the second, third and fourth missed periods. One mg. twice a week is the minimum dose. If bleeding occurs, active therapy of 5 to 10 mg. once or twice a day should be given.

Progesterone is of value in the true cases of threat-

ened abortion, but it is difficult to differentiate threatened and inevitable abortion due to the death of the fetus, when symptoms first arise. Profuse bleeding with cramps usually indicates inevitable abortion. Recurrent episodes of bleeding or bleeding of more than 7 days usually indicates inevitable or missed abortion if other pathology such as low implantation of the placenta or eroded cervix can be ruled out.

The critical period of pregnancy is the second and third months at which time the production of progesterone is taken over by the placenta.

Retained or delayed abortion may result from continued use of large doses of progesterone for bleeding.

The incidence of prematurity and developmental defects is higher than the normal expectancy in patients who bleed during their pregnancy.

REFERENCES

1. Fraenkel, L.: *Arch. f. Gynak.* 68: 438. 1903.
2. Corner, G. W., and W. M. Allen: *Amer. J. Physiol.* 88: 340. 1929.
3. Browne, J. S. L., J. S. Henry and E. H. Venning: *Amer. J. Obst. & Gynec.* 38: 927. 1939.
4. Irving, F. C.: *M. Rec. & Ann.*, 1938.
5. Taussig, F. J.: *Minnesota Med.* 21: 385. 1938.
6. Vogt, E.: *Munchen. med. Wchnschr.* 81: 791. 1934.
7. Ley, L.: *Munchen. med. Wchnschr.* 84: 1814. 1937.
8. Evans, H. M., and K. S. Bishop: *J. Metab. Research* 3: 201, 1923.
9. Sure, B. J.: *J. Biol. Chem.* 58: 693. 1924.
10. Hirst, J. C.: *Am. J. Obst. & Gynec.* 77: 662. 1918.
11. Da Re, O.: *Endocrinologia* 8: 623. 1933.
12. Shea, S.: *Brit. Med. J.* 1: 1053. 1933.
13. Reynolds, S. R. M.: Physiology of the Uterus, Paul B. Hoeber, N. Y. 1939.
14. Portman, K.: *Hospitalstid*, 77: 397. 1934.
15. Hall, G. J.: *Med. Rec.* 140: 207. 1934.
16. Saidl, J.: *Casop. lek cesk.* 73: 1247. 1934.
17. Smith, F. B., and R. A. Johnston: *Texas State J. M.* 30: 748. 1935.
18. Rodecurt, M.: *Deutsche med. Wchnschr.* 62: 1880. 1926.
19. Asjes, J. P.: *Nederl. tijdschr. v. geneesk.* 81: 1242. 1937.
20. Clauberg, C.: *Practitioner* 138: 634. 1937.
21. Vermelin, H.: *Bull. Soc. d'obst. et de gynec.* 28: 540. 1940.
22. Antechi, S., and T. Zwolinski: *Polska gaz. lek.* 2: 845. 1928.
23. Wolfsohn, H.: *Med. Welt.* 6: 1616. 1932.
24. Kane, H.: *Virginia Med. Monthly* 62: 334. 1935. *Am. J. Obst. & Gynec.* 32: 110. 1936.
25. Krohn, L., F. H. Falls and J. E. Lackner: *Am. J. Obst. & Gynec.* 29: 198. 1935; *J.A.M.A.* 106: 271. 1936.
26. Bishop, P. M. F.: *Guy's Hosp. Rep.* 87: 362. 1937.
27. Gershenfeld, D. B.: *J. M. Soc. New Jersey* 34: 508. 1937.
28. Elden, C. A.: *Am. J. Obst. & Gynec.* 35: 648. 1938.
29. MacGregor, T. N., and C. P. Stewart: *J. Obst. & Gynec. Brit. Emp.* 46: 857. 1939.
30. Campbell, R. E., and E. L. Sevringhaus: *Am. J. Obst. & Gynec.* 39: 573. 1940.
31. Huber, C. P.: *Am. J. Obst. & Gynec.* 39: 573, discussion. 1940.
32. Mazer, C., and S. L. Israel: Diagnosis and Treatment of Menstrual Disorders and Sterility. Paul B. Hoeber, N. Y. 1941.
33. Krohn, L., and J. H. Harris: *Am. J. Obs . & Gynec.* 41: 95. 1941.
34. Collins, C. G., J. C. Weed and H. J. Collins: *Surg. Gynec. & Obst.* 70: 783. 1940.
35. Tholen, M. H. G. A., and L. A. M. Stolte: *Nederl. tijdschr. v. geneesk.* 83: 3880. 1939.
36. Feiman, D. T.: *Ohio State Med. J.* 35: 288. 1939.
37. Mott, F. P.: The Wistar Institute of Anatomy and Biology, pp. 1, 12, 28. Philadelphia. 1908.
38. Shute, E.: *Am. J. Obst. & Gynec.* 35: 810. 1938.

COMMUNICATIONS TO THE EDITORS

Adequacy of Iodized Salt for Goiter Prevention*

FOLLOWING THE DEMONSTRATION[1] that colloid goiter could be prevented or cured by use of small doses of iodine given during childhood and adolescence there arose a suspicion that universal use of iodine by the population in the 'goiter belt' might be dangerous. This was because of fear that an induced thyrotoxicosis would follow[2] in a significant number of adults. This fear has been dispelled in most quarters[3,4] by the experience of the past quarter century. During this time iodine has been used on personal prescription, administered in tablet form to school children in large groups, and has been made available to the entire population of certain urban areas by iodization of water supplies. The most popular form of iodine supply has become the iodized table salt which is now provided by most manufacturers of salt as an alternate form of boxed or bag salt. Two further criticisms of this form of iodine supply have been expressed, that the iodine content of such salt may be variable and unstable,[5] and that dependence upon such a source of iodine may not provide adequate amounts for small children who add no salt voluntarily to their food. The work reported herewith is to contribute to the answer which can be given to this latter question.

A study of urinary iodine excretion will provide information about the amount of iodine available to the individuals examined. It has been shown[6] that urinary iodine parallels iodine intake, and in healthy individuals is the largest factor in iodine excretion. In goitrous regions iodine excretion is lower than in non-goitrous areas. It has been shown[7,8] that during pregnancy the use of iodized salt provided adequate amounts of iodine. The iodine excretion of a group of children in a goiter area such as Wisconsin, selected from homes where all table and cooking salt in use was iodized salt, should provide data for decision as to the adequacy of iodized salt as the chief source of iodine in childhood. Therefore, such observations were made on 10 children, varying in age from 1.7 to 12 years, choosing children from the homes of a number of physicians in different parts of the state who were able to assure us that urine collections were complete and not contaminated, that only iodized salt was in use, and that the child was not aware of being observed as to salt intake and its correlated iodine supply.

The 24-hour-urine samples were colllected in clean glassware supplied for the purpose. Analysis was carried out by one observer only, following the method of Mathews, Curtis and Brode.[9] The results are presented in tabular form. A wide variation in amounts of iodine is to be expected. The scatter from 53 to 594 micrograms per 24 hours is not surprising in comparison with data reported from other laboratories. The marked differences between determinations of different 24-hour samples from the same child are similarly expressive of the well known variation in the intake and output of NaCl.

IODINE EXCRETION IN CHILDREN USING IODIZED SALT

Age in years	Iodine excretion in micrograms per 24 hours
1.7	53
	74
2.8	550
	488
4	108
5	165
5.5	58[1]
	238
6-8	78
7-9	281
	411
10	594
12	138
	69
12	271

Extremes: 53 to 594. Average: 238.

[1] On this day the mother knows no salt was used in preparation or serving this child's food.

* The cost of technical work and transportation of specimens was defrayed by a grant from the Committee on Goiter Prevention of the State Medical Society of Wisconsin.

[1] MARINE, D.: *J.A.M.A.* 87: 1463. 1926.
[2] MÜHE, ILSE: *Deutsches Arch. f klin. Med.* 177: 345. 1935.
[3] MCCLURE, R. D.: *J.A.M.A.* 109: 782. 1937.
[4] KIMBALL, O. P.: *J.A.M.A.* 108: 860. 1937.
[5] NICHOLS, M. S.: *Am. J. Pub. Health* 19: 923. 1929. COWRIE, D. M. AND ENGELFRIED, J. J.: *J. Mich. Med. Soc.* 39: 784, 1940.
[6] CURTIS, G. M., PUPPEL, I. D., COLE, V. V. AND MATHEWS, N. L. *J. Lab. & Clin. Med.* 22: 1014. 1937.
[7] ENRIGHT, L., COLE, V. V. AND F. A. HITCHCOCK: *Am. J. Physiol.* 113: 221. 1935.
[8] WESPI, H. J.: *Schweiz. med. Wchnschr.* 70: 926. 1940.
[9] MATHEWS, N. L., G. M. CURTIS AND W. R. BRODE: *Indus. & Eng. Chem.* 10: 612. 1938.

There is no distinct age trend to higher iodine excretion. The minimum value recorded is 53 micrograms, which is of the same order of magnitude as the findings of Curtis and his associates[6] in Ohio subjects, using similar analytic methods. Among males in the first decade, in a goitrous region, he found an average of 41 micrograms per day. The average iodine excretion in nongoitrous regions is reported by the same investigators as 165 micrograms. It is suggested by Curtis[10] and others[11] that an excretion of 50 micrograms per day represents approximately the lower level of normal iodine need. Therefore, the results reported here appear to indicate that use of iodized salt by children leads to intake of amounts of iodine fully adequate for prevention of goiter. Even though this series of cases is small, the number of specimens per subject only one or two each, and the variations wide, the general levels of iodine excretion seem well above any dangerously low margin. It is concluded that the use of iodized salt by families will provide adequate iodine intake for the needs of most children. If the physician considers additional iodine necessary temporarily, due to rapid growth or increased demands on the thyroid during acute infection, there is no difficulty in prescribing such iodine to meet the need.

Of course there are further problems requiring attention in the manufacture and sale of iodized salt. The amounts of iodide to be added, the use of further additions to the salt for other purposes in control of quality of shaker salt, and the uniformity of iodine content during the time between manufacture and eventual use require attention. Some students of these questions[11] advise use of salt with only 1 part of iodine per 100,000 of salt. Daily intake of 50 micrograms of iodine would depend on use of an average of 5 gm. of such salt daily. Many adults do not use this amount, and certainly not all children will have an adequate iodine intake under such conditions. Some of the most commonly used brands of iodized table salt in the United States at present contain 1 part of iodine per 5000, of salt. With this concentration, the use of only 1 gm. of salt per day provides an intake of 200 micrograms, which is well above the margin of need for goiter prevention. It would be necessary to limit salt intake very drastically to keep the daily total as low as 1 gm. daily. Consequently, it seems probable that salt with only 1 part of iodine per 10,000 parts of NaCl will be able to provide an abundance of iodine for prevention of goiter. It is suggested that since prevention of goiter is a health measure of importance to the entire population in many states of this country, and since iodized salt is not only convenient, safe, and economical but also effective and dependable, the control of iodine content of salt should become a function of state health authorities.

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[10] CURTIS, G. M.: *Surg., Gynec. & Obst.* 62: 365. 1936.
[11] EGGENBERGER, H., AND F. M. MESSERLI: *West. J. Surg.* 47: 596. 1939.

Anogenital Pruritus in the Male Climacteric: Treatment with Testosterone Propionate

THIS COMMUNICATION concerns anogenital pruritus which occurred as a part of a syndrome described as male climacteric;[1,2] this pruritus was successfully treated by the administration of testosterone propionate.* Since recent perusals of the literature revealed no recorded evidence to show that pruritus ani in the male of the climacteric age is the result of a deficiency of testis hormone, these cases are described in detail.

Case 1. A 54-year-old, white, married man, was seen Jan. 14, 1940, because of pruritus ani and perinei of 4 years' duration which had been refractory to topical and radiation therapy. During the past 7 years there were noted progressive nervousness, inability to concentrate on business and domestic problems, and exaggerated worry over trivial matters. Coincident with these changes there appeared fatigue to the point where he had to abandon all forms of exercise except moderate walking, and a gradual loss of libido which at first was attributed to general fatigability. Although he had no difficulty in falling asleep, the patient awakened after 3 to 4 hours and found it extremely difficult to resume his sleep. During these wakeful hours, he experienced, palpitation, tachycardia and a frequent desire to urinate. Subsequently, pruritus of the perianal, perineal and scrotal areas of increasing severity developed at night. During the past 2 years, refractory localized pruritus (especially in the perianal region) was present night and day. He lost weight and become somewhat despondent. (During the course of the interview, he wept several times.)

The past history disclosed that the internal hemorrhoids had been treated by injections of sclerosing solutions 6 years previously.

The physical examination revealed mild peripheral arteriosclerosis, tachycardia varying from 92 to 100 beats per minute, systolic blood pressure of 150 mm. of mercury and a diastolic of 90, a slightly enlarged but uniform and

[1] WERNER, A. A.: *J.A.M.A.* 112: 1441. 1939.
[2] DOUGLAS, R. J.: *J. Urol.* 45: 404. 1941.
*Supplied by Dr. W. H. Stoner of the Schering Corp., Bloomfield, N. J.

impressionable prostate, small internal hemorrhoids and scratch marks about the perineum and perianal region without thickening or induration of the skin. The testicles appeared normal in size and consistency. The urine findings were normal. The blood count and the sedimentation time were within normal limits. The blood Wassermann reaction was negative. The prostatic secretion showed a few leukocytes per high power field. The basal metabolic rate was +1 and −4 on two different occasions.

Testosterone propionate therapy was begun Feb. 2, giving 25 to 35 mg. weekly until a total of 235 mg. was administered. Following this course of treatment, his subjective complaints including localized pruritus had disappeared. About ten weeks after the cessation of endocrine therapy, there developed gradual decrease of libido, an increase of fatigability (especially toward the end of the day) and disturbance of sleep. The patient was given placebos in the form of biweekly injections of 1 cc. of sesame oil for 2 weeks without improvement. Testosterone propionate therapy was then resumed.

Case 2. (Reported through the courtesy of Dr. H. Feldman.) *A.M.*, a 52-year-old white man was seen Dec. 9, 1937, because of gradual loss of libido, failing memory and severe pruritus ani which did not respond to various forms of treatment. The past history included syphilis which was treated in 1915. Physical examination was normal throughout; no signs of latent syphilis were discernible. The urine findings were normal and the basal metabolic rate was −13%. Small doses of desiccated thyroid had no effect on the pruritus ani. In March 1938, 10 mg. of testosterone propionate were given every other day. After the administration of a total of 120 mg. of male sex hormone there was definite improvement in the libido as well as in the anal pruritus. Similar courses of male sex hormone therapy were repeated several times during 1938 and were always followed by improvement in the libido and the cessation of pruritus ani. After an absence of 7 months, the patient returned in July 1939, with a recurrence of loss of libido and pruritus ani; this time he also complained of a weak urinary stream and occasional terminal dribbling. He was then given 25 mg. of testosterone propionate every other day for 12 doses. General improvement was marked and was followed by cessation of pruritus ani and improvement in the urinary symptoms. In January 1940, the patient again had marked anal itching which again responded to testosterone propionate therapy.

Summary. Circumanal and perineal pruritus occurring in 2 men of the climacteric age was successfully treated by the administration of testosterone propionate. Therapeutically, the androgens in the absence of other therapy were as effective in these patients as the estrogens are in the treatment of genital pruritus of menopause of some women.

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Near-Fatal Reaction to Pregnant Mare Serum

A PATIENT, *Mrs. C. L. L.*, aged 24, consulted me for the first time in April 1940. Her chief complaint was sterility, dating from her marriage four years previously. Her family history was interesting in that the fecundity was unusually high. The patient was the fifth of nine living children and she had four sisters, all of whom had become pregnant soon after marriage. The social history was irrelevant and the patient stated that she had suffered from no serious medical diseases. Two of her sisters suffered with seasonal hay fever and the patient stated that she had had urticaria after eating strawberries. However, even this allergic condition had not been observed for several years. The menarche occurred at the age of 13 years and she had menstruated at regular intervals of 28 to 30 days since that time. The flow was normal, lasted about 5 days, and there was no dysmenorrhea.

The general physical examination revealed a normally developed young woman, weighing approximately 120 pounds. No physical anomalies could be found other than a strabismus which dated from an ocular injury some years previously. The red blood count was 4,500,000; the white blood count 8,200; and the urine findings were normal. The pelvic examination revealed a normal vagina, a small nulliparous cervix directed posteriorly; and the uterus was anterior, normal in size, and freely movable. The tubes and ovaries were not palpable. The PH of the vagina was 4.7. A Rubin test showed that the tubes were patent at 150 mm. of mercury. A biopsy of the endometrium was taken in May 1940 on the day before the expected menses and a persistent proliferative phase was found. Examination of the husband's seminal fluid showed that it was normal in amount, and the motility and morphology were within normal limits. The diagnosis of anovulatory sterility was made. Beginning on the sixth day of the May 1940 menses 1 cc. of pregnant mare serum (Gonadin, 200 R.U.) was given intravenously and repeated on the eighth, tenth, twelfth, thirteenth, and fourteenth days of the cycle. An intradermal skin test was made prior to the first injection and no reaction was obtained. The patient experienced no reaction from this intravenous therapy and menstruated at her regular time in June 1940. Therapy with mare serum gonadotropin was again started on the sixth day of her cycle and repeated on the eighth, tenth, twelfth, thirteenth, and fourteenth days. The patient missed her menses in July 1940 and was seen in Septem-

ber at which time she was two and a half months' pregnant. Spontaneous abortion of a 4 cm. fetus occurred in October.

In May 1941 the patient was seen again with a history of having menstruated regularly since the abortion, and she again desired treatment to become pregnant. No further examination was made at this time and she was told to return on the sixth day of her next cycle. On June 2, 1941 the patient was given 1 cc. of the mare serum gonadotropin (200 R.U.) intravenously without a preliminary skin test. Several minutes after the injection the patient complained of feeling dizzy and asked to lie down. By the time she could be removed to another room and placed on the table, the patient was semi-conscious. The skin became cold and clammy, the pulse at the wrist could not be felt, and the respirations were short and labored. The skin developed a peculiar mottled appearance and the mucous membrane of the mouth became edematous. The tongue was swollen to at least twice normal size. Epinephrin, 1 cc. was given subcutaneously. Since respiration was rapidly becoming obstructed by the edema of the tongue and pharynx, an airway was promptly inserted. Hot blankets were applied and artificial respiration was instituted. The blood pressure could not be recorded. Fifteen minutes after giving the patient epinephrin, the pulse became palpable, blood pressure was recorded at 70 systolic and the edema began to subside. After 60 minutes the patient began to arouse from her stupor. Three hours after the initial shock the patient was able to be moved to her home in an ambulance.

Experience with over 200 injections of mare serum gonadotropin (Gonadin), 92 of which have been given intravenously, has impressed me with the potency, safety, and clinical value of this hormone. This case is the only serum reaction which I have seen. It would not have occurred if the patient had been skin tested before resuming therapy. It is now my practice to skin test every patient before each injection of this hormone. The last 74 consecutive skin tests have disclosed 5 positive reactors. Therapy has been withheld in these patients.

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Abstracts of

CURRENT CLINICAL LITERATURE

Editor: HANS O. HATERIUS. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, ARTHUR GROLLMAN, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. C. PFEIFFER, GEORGE W. THORN EMMERICH VON HAAM.

ADRENALS

HURST, A., AND S. L. SIMPSON.

Adrenal grafts in Addison's disease.—Two letters. *Brit. M. J.* I: 870. 1941.

Hurst describes a case, accepted as a typical case of Addison's disease, apparently cured by grafting the adrenal of an infant immediately after its death into the patient's testicle. The man died 2 years and 3 months after the operation, apparently from Addison's anemia. Postmortem showed perfectly healthy adrenal glands and no trace of adrenal graft tissue. Simpson states that his limited experience with adrenal grafts is that the effect is only temporary or negative. Subcutaneous implantation of desoxycorticosterone tablets is effective for 4 months or longer and can be repeated. One must remember, however, that this is not the only hormone of the adrenal gland. Absence of obvious pigmentation does not necessarily exclude the possibility of Addison's disease, but lack of pigmentation, without characteristic changes in Na metabolism is a doubtful case.—*J. B. Paton.*

ENDOCRINE GENERAL

CHRISTIE, A. U., E. C. DUNHAM, R. M. JENSS AND A. L. DIPPEL.

Development of the center for the cuboid bone in newborn infants. A roentgenographic study. *Am. J. Dis. Child.* 61: 470. 1941.

In a study of the osseous development of 1,107 newborn infants, both white and colored of both sexes, roentgenograms within 72 hours of birth showed association of the presence of the center of ossification for the cuboid bone with race and sex, with certain often used criteria of the maturity of the infant and with the parity and age of the mother. The center was found to be present more frequently in negro than in white children of the same sex, and in girls more than in boys of both races. It was more frequent in infants judged to be more mature on the basis of birth weight, crown-heel length at birth and gestational ages. The centers were more advanced in infants born to multiparae than in those born to primiparae and in those infants born to older women than to younger women.—*M.B.G.*

MASON, H. H., AND DOROTHY H. ANDERSEN.

Glycogen disease. *Am. J. Dis. Child.* 61: 795. 1941.

A case of glycogen-storage disease is reported which was characterized by a defect in the enzyme of the liver responsible for breakdown of glycogen into dextrose and formation of glycogen from dextrose. A classification of cases of excessive glycogen storage into 5 groups is presented, each dependent on a different fundamental defect and separable by clinical and pathological criteria.—*E.R.M.*

SEVRINGHAUS, E. L.

Endocrine glands and dermatology. *Semana méd.* 1: 989. 1941.

A review.—*A.E.M.*

STEINER, M. M., AND A. L. NEWCOMB.

Enlargement of the thyroid gland in juvenile patients with diabetes mellitus. Incidence of diabetes and thyroid disease in the family. *Am. J. Dis. Child.* 61: 459. 1941.

The authors found a palpable thyroid gland in 20% of 128 juvenile diabetic patients. A study of the family history showed that 50% of the diabetic children with palpable thyroid had a family history of diabetes and 80% a family history of thyroid disease. In comparison with this, in diabetics with a normal thyroid gland, there was a family history of diabetes in 19% and of thyroid disease in 12%. Two personal cases of diabetes with hyperthyroidism in children are reported. The onset of diabetes occurred in the children at about the same age, the thyroid gland became palpable early in the course and the mothers had each been subjected to thyroidectomy before the birth of the patients. There was no diabetic history in either. In a third case, a girl of 10 years presented symptoms of probable diabetes. The association of hyperthyroidism and diabetes mellitus appears to produce a change in the diabetic state as characterized by persistent glycosuria and failure of the patient to do well with a controlled diet and insulin, necessitating an increase in the dosage of the latter. A differential diagnosis is given between hyperthyroidism with hyperglycemia and diabetes mellitus with hyperthyroidism.—*M.B.G.*

VESELL, M., AND S. GOLDMAN.

Friedman tests on spinal fluid in cases of hydatidiform mole and pregnancy. *Am. J. Obst. & Gynec.* 42: 272. 1941.

Friedman tests on spinal fluid were positive in 2 cases of hydatid mole; negative in a cured case of hydatid mole; negative in 1 case of ectopic pregnancy; negative in early and late normal pregnancies; negative in pregnancies complicating myomata and ovarian cysts; positive in a male with seminoma.—*E.C.H.*

GONADS

ALBRIEUX, A. S.

Concentration of estrogenic hormones in blood serum and blood cells. *Proc. Soc. Exper. Biol. & Med.* 47: 381. 1941.

The blood serum and blood cells of a group of 20 non-pregnant women were examined for estrogenic hormone content by the intravaginal application of pellets made from desiccated material. The blood cells contained 2 or more times as many R.U. per unit volume as the blood serum.—*Author's abstract.*

ALBRIEUX, A. S.

Estrogen content of the blood at four-hour intervals. *Proc. Soc. Exper. Biol. & Med.* 47: 380. 1941.

The estrogenic hormone content of the blood of women was determined at 4-hour intervals during the course of one day in 5 instances. A significant diurnal rise was noted once, a minor increase in 3 cases, and a constant level was found in one case.—*Author's abstract.*

ALBRIGHT, F., ESTHER BLOOMBERG AND PATRICIA H. SMITH.

Post-menopausal osteoporosis. *Tr. A. Am. Physicians* 55: 298. 1940.

Estrin therapy is effective in restoring a positive Ca and P balance in women with post-menopausal osteoporosis.—*M. L. C. Bernheim.*

AUB, J. C., AND I. T. NATHANSON.

The value of sex hormone assays in differential diagnosis of puberty. *Tr. A. Am. Physicians* 55: 306. 1940.

The excretion of the sex hormones parallels the physical development rather than the actual age of the child. Thus assay of the sex hormone excretion is a valuable aid to diagnosis.—*M. L. C. Bernheim.*

BÜTTNER, W., AND R. TROPPMANN.

Influence of progesterone on the excretion of the gonadotropic hormone in the urine of women during menopause. *Arch. f. Gynäk.* 170: 413. 1940.

Administration of synthetic progesterone to 2 women during pregnancy caused no change in the excretion of the gonadotropic hormone from 6 to 8 days later. Dihydroxydiethylstilbene produced a decrease in the posterior lobe hormone of the pituitary gland in the urine of one case which could not be compensated by progesterone.—*E. Kaufmann.*

BUXTON, C. L.

The effects of certain gonadotropic extracts on anovulatory cycles and amenorrhea. *Am. J. Obst. & Gynec.* 42: 236. 1941.

Ten patients, judged to have anovulatory bleeding by studies of repeated endometrial biopsies and pregnandiol determinations, were treated. The majority received equine gonadotropin; a few were given chorionic gonadotropin and whole pituitary synergist ('synapoidin'). Equine gonadotropin, as a rule, was administered during first two weeks of the cycle in 4 doses of 200 Cole-Saunders U. each. The author believes ovulation may have been induced in 4 of these patients; no pregnancies occurred. Ten patients with amenorrhea, likewise judged anovulatory, were treated. Two of these are thought to have responded. One bled irregularly for at least 1 year after equine gonadotropic therapy. Another diagnosed as having a 'primary pituitary insufficiency' became pregnant after therapy with the chorionic gonadotropin and pituitary synergist.—*E.C.H.*

DE LAAT, B. M.

Colorimetric estimation of male substances in urine. *Acta. brev. Neerland.* 11: 51. 1941.

The benzene extract of urine from males or females is divided into androsterone and dehydroandrosterone fractions by chromatographic adsorption, for which Al_2O_3 is used. Colorimetric estimation of each fraction makes it possible to calculate the biological potency of the extract.—*Author's abstract.*

DENNIS, W.

Effect of pubertas praecox on the age at which onset of walking occurs. *Am. J. Dis. Child.* 61: 951. 1941.

An analysis is made of the onset of walking in 25 children in the literature who attained puberty in the first 2 years of life. Only cases due to hyperactivity of the gonads are included. The range of the onset of walking in these cases was from 9 to 18 months, with a mean of 13.58, which is within normal limits. It is concluded that over-development of size, strength and ossification before the normal onset of walking does not affect the latter.—*M.B.G.*

EAGLE, E.

Blood choline variations in pregnancy, in labor and in the puerperium. *Am. J. Obst. & Gynec.* 42: 262. 1941.

Using a method previously described, 124 choline determinations were made on blood samples from 62 women in various stages of pregnancy, 17 women in labor, 8 in the puerperium, 19 non-pregnant women and 18 males. Choline content of blood from pregnant women from 207 days before delivery to term was fairly constant (average 13.1 mg./liter); the value was slightly increased during

labor (average 15.0 mg./liter); the choline level was highest just after delivery (average 24.6 mg./liter); an average of 14.6 mg./liter was obtained for the choline content of blood from non-pregnant female patients and of 13.4 mg./liter for males. The possible endocrine associations of choline and its rôle in onset of labor are discussed.—*E.C.H.*

Effkemann, G., and E. Werle.

The significance of the histamine metabolism in the pregnant and nonpregnant organism. *Arch. f. Gynäk.* 170: 173. 1940.

In the nonpregnant human and animal uterus a high content of histamine is found, but in pregnancy this substance is greatly reduced; considerable histaminase, which destroys histamine, is found in the blood and uterus. Therefore the histamine level in the blood of gravid women remains low. In the fetal circulation of the placenta, histaminase activity is very great and the histamine level low. The metabolism of the embryo liberates much histaminase and this appears in the fetal blood, but owing to the protection of the newborn by the histaminase, this histamine level is not increased. After expulsion of the placenta the histamine content is high and probably of importance in the regulation of labor and pain.—*E. Kaufmann.*

Geist, S. H., R. I. Walter and U. J. Salmon.

Are estrogens carcinogenic in the human female? Atypical endometrial proliferation in a patient treated with estrogens. *Am. J. Obst. & Gynec.* 42: 242. 1941.

This case report concerns a 52-year-old woman treated with large doses of estrogens during a 2-year period. An inventory of the estrogens given includes: 274,000 R.U. of estradiol benzoate by injection and the implantation of a 25 mg. pellet of estradiol and of 29 mg. of loose crystals of estradiol benzoate. During this time 7 endometrial and vaginal biopsies showed no abnormal cytologic alterations. Subsequently a curettage was done because of abnormal bleeding. Two pathologists considered the endometrium obtained to be benign; 3 others thought it represented an early adenocarcinoma. Hysterectomy was done 8 days later; endometrium at this time showed no evidence of carcinoma or metaplasia.—*E.C.H.*

Glueck, H. I., and I. A. Mirsky.

The clotting mechanism of menstrual fluid. *Am. J. Obst. & Gynec.* 42: 267. 1941.

Menstrual blood of 9 healthy women was studied for content of fibrinogen, prothrombin, thrombin and anticoagulants. No detectable amounts of these were found. The significance of these findings is discussed. It is suggested that the blood leaving the endometrium may clot, the clot ultimately undergoing digestion by some hypothetical lytic agent and that, when bleeding is excessive, the rate of this supposed lysis may be relatively slow with the result that undigested clots are passed.—*E.C.H.*

Greene, R. R., and J. I. Brewer.

Relation of sex hormones to tumors of the female reproductive system. *Am. J. Roentgenol.* 45: 426. 1941.

The authors review the literature on laboratory and clinical data regarding the production of tumors by sex hormones. They conclude that while the cause of certain tumors in certain animals is definitely established, there is not sufficient evidence to believe that any one factor, such as estrogens, is the sole important etiological agent in the production of any tumor of the human female. An extensive bibliography is appended.—*E. H. Quimby.*

Huffman, J. W.

New factors of clinical significance in the study of human spermatozoa. *Surg., Gynec. & Obst.* 73: 228. 1941.

As the number of spermatozoa per cc. of human seminal fluid decreases, the percentage of abnormal forms increases.—*A.T.K.*

Jones, H. O., and J. I. Brewer.

A study of the ovaries and endometriums of patients with fundal carcinomas. *Am. J. Obst. & Gynec.* 42: 207. 1941.

The ovaries and endometrium of 68 patients with fundal carcinoma, who were treated surgically without preoperative irradiation, were studied. Nineteen of these 68 patients were premenopausal. Eleven had cyclic menses. Nine of the 11 had been operated upon between the 14th and 25th days of the cycle: the ovaries of 8 contained functional corpora lutea, and the endometrium, except where involved by the malignant process, showed normal endocrine responses, none showing 'cystic hyperplasia.' 'Cystic glandular hyperplasia' was found in only 2 of the 68 cases. 'Cystic changes' in the ovaries occurred in 8 of the premenopausal and in 1 of the postmenopausal patients; in the former 8 patients cyclic ovarian responses occurred despite 'cystic changes.' In fundal carcinoma ovaries and the uninvaded endometrium may function normally from the endocrine point of view and no etiologically significant rôle of hyperestrinism or unopposed estrogenic action was demonstrated.—*E.C.H.*

Kneer, M.

The oxytocic action of follicle hormone on the muscle of the human uterus. *Arch. f. Gynäk.* 170: 483. 1940.

Follicle hormone increases the size of muscle fibers and interstitial tissue in the uterus. During the menstrual cycle it does not exhibit an oxytocic action. The uterus is sensitized for the pituitary hormone of the posterior lobe at the time of menstruation when the follicle hormone is excreted. Lack of the latter decreases the susceptibility for the posterior lobe hormone. Because of the influence exerted by the follicle hormone and the corpus luteum, neurohormonal factors are of importance. The corpus luteum and the gonadotropic chorionic hormone decrease the tension and the contractility of the muscle fiber, but the follicle hormone does not exert any oxytocic effect upon the gravid uterus. Labor begins on termination of the growth of the uterus, and its muscle fibers and interstitial tissue. Then at the end of pregnancy the anterior lobe hormone of the pituitary gland induces contractility of the uterus muscle and the follicle hormone now deprived of any function is disposed of by excretion in the urine.—*E. Kaufmann.*

MURPHY, D. F.

The contractile response of the human uterus to posterior pituitary extract administered at regular intervals during pregnancy. *Surg., Gynec. & Obst.* 73: 175. 1941.

Recording by Lorand tocograph applied to abdominal wall. Thirty-two subjects received 1 to 3 minims obstetrical pituitrin at various times in pregnancy. Responses were detected after 25th week but there was a wide variation in time of appearance. In a patient with marked uterine tension before injection prolonged painful spasm was produced by the pituitrin. It is suggested that the state of initial tone determines the intensity of response. Evaluation of this tone may forestall accidents from the use of pituitrin at the time of labor.—*A.T.K.*

PAPANICOLAOU, G. N., AND H. F. TRAUT.

The diagnostic value of vaginal smears in carcinoma of the uterus. *Am. J. Obst. & Gynec.* 42: 193. 1941.

Method of securing and staining vaginal smears is described in detail. Descriptions are given of the vaginal cytology in association with carcinoma of cervix and of uterus. The authors believe they can recognize cells in vaginal smears pathognomonic of cervical and fundal carcinoma, even in some very early cases. They caution that the interpretation of the smears under these circumstances 'requires the services of a careful and discriminating cytologist who has had experience in this field.'—*E.C.H.*

PAYNE, F. L.

Hormone studies in the presence of hydatidiform mole and chorionepithelioma. *Surg., Gynec. & Obst.* 73: 86. 1941.

In determining the value of hormone analysis in the diagnosis of hydatidiform mole and chorionepithelioma the curve of gonadotropic concentrations during normal pregnancy was employed as a standard. Studies showed that any of 4 types of mole activity may occur. Following evacuation of the mole, regularly spaced hormone titrations for a year were necessary to differentiate between recovery and development of chorionepithelioma. An increase in values denoted presence of malignant degeneration or intervening pregnancy, whereas a gradual decline or lack of increase, indicated absence of chorionepithelioma. For diagnostic purposes, repeated quantitative titrations are valuable as any final decision should be based not upon a single qualitative or quantitative determination but upon demonstration of increased values over a short period.—*H.O.H.*

REYNOLDS, S. R. M., S. KAMINESTER, F. I. FOSTER AND S. SCHLOSS.

Dermavascular effects of estrogen in women with menopausal flushes. *Surg., Gynec. & Obst.* 73: 206. 1941.

The authors describe the changes in finger volume induced by estrogens in menopausal women with hot flushes before and after relief of the symptoms by estrogens, psychotherapy or sedatives. Estrogens induce an increase in finger volume which may be gradual (plateau type) or acute (flush type). In the latter form a rise in skin temperature and sensation of warmth occurs. The natural menopausal flush is similar from the standpoint of peripheral mechanism to the estrogen flush. Before relief of symptoms the menopausal woman reacts to estrogens more frequently with a flush response, after relief flush responses are less prominent and no response at all is often observed. The differences are most conspicuous in women treated by psychotherapy. This paper is one of an important series describing the vasomotor effects of the estrogens and the vasomotor instability of the menopause. The paradox that a substance which itself induces vasodilatation should ameliorate symptoms of essentially the same type is a paradox which must be borne for the present.—*A.T.K.*

SMITH, E. R.

An investigation of the action of manganese on the uterus pertinent to its use in dysmenorrhea. *Yale J. Biol. & Med.* 13: 623. 1941.

In concentrations below 1 mg.% $MnCl_2$ increased the response of the rat uterus to pitocin. Above this amount Mn depressed uterine contraction. Alone, Mn had no effect on spontaneous uterine contractions. It is suggested that the alleged effectiveness of Mn in relieving dysmenorrhea may depend on an interaction with pitocin or some similar hormone with resulting alteration in the internal respiration of uterine muscle.—*G. H. W. Lucas.*

TIEN, D. S. P.

The significance of pregnanediol in pregnancy urine. *Chinese M. J.* 59: 416. 1941.

The excretion of pregnanediol by pregnant Chinese was similar to that found in Western countries. Isobutanol extracted 64% as much pregnanediol from urine as did normal butanol by Venning and Browne's 1937 technic.—*C. D. Stevens.*

WAGNER, D.

Local treatment of chronic cutaneous ulcers with stilbestrol: vascular efficacy of synthetic estrogens. *Arch. f. Dermat. u. Syph.* 181: 395. 1940.

In view of the efficacy of hormonal substances in treatment of disturbances of peripheral circulation in women at puberty, during pregnancy and at the menopause and during periods of hormonal dysfunction, and from use of ovarian preparations in acrocyanosis, Raynaud's disease, endarteritis obliterans, ulcus hypostaticum and gastrointestinal ulcers, stilbestrol was used locally on various types of resistant ulcers associated with severe vascular changes. Cyren A, B, C, Oestromon and Cyren A- and Oestromon ointments were also used. One to two ampules of the oil solution were applied locally daily and allowed to be absorbed. After epithelialization had started an ointment was used. The author attributes beneficial effect in the 9 cases studied to action of the estrogens on the blood vessels.—*S. W. Becker.*

WERLE, E., AND G. EFFKEMANN.

The destruction of histamine by the blood of pregnant women. *Arch f. Gynäk.* 170: 82. 1940.

Blood of pregnant women considerably inactivates histamine. The condition begins in the early months in pregnancy, increases up to the 7th month and then decreases until the end of pregnancy. In the 3rd month the action of the blood is 3.5 times and in the 6th month 20 times as high as in non-pregnant women. This destruction of histamine is typical in pregnancy, but not found in various diseases. It is due to histaminase in the blood and organs.—*E. Kaufmann.*

WOBKER, W.

The oxytocic effect of follicle hormones, visualized by x-rays, on the uterus of rabbits. *Arch. f. Gynäk.* 170: 301. 1940.

After subserous injection of 40% iodipin into the uterus of rabbits in 8 of 9 animals, uterine contraction is demonstrated on intravenous injection of various brands of follicle hormone, including stilbestrol in 3 cases. The results are similar to those recorded with ball insertion and manometric registration.—*E. Kaufmann.*

WOLFE, S. A., AND I. NEIGUS.

Theca cell tumors of the ovary. *Am. J. Obst. & Gynec.* 42: 218. 1941.

The clinical and pathologic findings in 8 cases of theca cell tumors of the ovary are reported.—*E.C.H.*

ZELLER, E. A., AND H. BIRKHÄUSER.

Chemical test for pregnancy. *Schweiz. med. Wochschr.* 70: 975. 1940.

The concentration of diamine oxidase (identical with histaminase) of serum is manometrically measured by determining the O_2 consumption during reaction with 0.01 M cadaverine. During pregnancy the enzyme content is .05-.19 unit, an increase over the normal content. A unit is the enzyme content of 1 gm. of substrate which oxidizes 10^{-6} mol. in 1 hour.—*M. M. Rath.*

HYPOPHYSIS

WILKINS, L.

Epiphysial dysgenesis associated with hypothyroidism. *Am. J. Dis. Child.* 61: 13. 1941.

Epiphysial dysgenesis was found by the author in 23 of 25 children with hypothyroidism, affecting all centers of endochondral ossification. The condition was present in all cartilages which began to ossify during the course of treatment as well as in those which had ossified previously. Only those centers showed dysgenesis in which there was delayed ossification because of the hypothyroidism. The condition is found only in hypothyroidism, according to the author, and is manifested in roentgenograms by the appearance of multiple irregular islets of ossification in the cartilages over a large area. These enlarge and coalesce to form an irregular, spongy porous or fluffy mass. Osteochondritis deformans of the hip which is a destructive lesion in a normally formed epiphysis simulates epiphysial dysgenesis which is an abnormality in endochondral ossification.—*M.B.G.*

WILKINS, L.

Recent studies on the diagnosis of hypothyroidism in children. *Pennsylvania M. J.* 44: 429. 1941.

This paper is a brief discourse on the diagnosis of typical and atypical thyroid underfunction in children. Defective skeletal growth and development are characteristic. Hair and skin and even subcutaneous tissues may not be tangibly altered. Stunted growth is constant, and if the child has been neglected, permanent dwarfism may result. The naso-orbital configuration remains infantile, the nose remaining short, its bridge broad and flat. There is delay in ossification of cartilaginous centers. Other features are defective dental development, epiphyseal dysgenesis (confirmed by x-ray), and retarded and defective brain development. Under certain circumstances hypothyroidism in children may evince no anatomic changes. This is possible if the subthyroidism has been transient, or if specific treatment had been instituted fairly early. Other clinical points in the average juvenile patient are mental and physical sluggishness, a lowered B.M.R., a cholesterol finding between 250 and 600 mg.% and a satisfactory response to the therapeutic test, i.e., a standard dose of thyroxin or thyroid.—*I.B.*

WOHL, M. G., AND N. PASTOR.

Hyperthyroidism at the menopause. *Am. J. Obst. & Gynec.* 41: 792. 1941.

The authors consider problems in the differential diagnosis of hyperthyroidism at the climacteric and syndromes due solely to estrogenic deficiency and in the respective therapeutic approaches to those conditions. Six illustrative case reports are given.—*E.C.H.*

WOODRUFF, P.

The behavior of the blood platelets in thyrotoxicosis. *M. J. Australia* 27: 190. 1940.

In 20 cases of thyrotoxicosis the mean number of white blood cells and of blood platelets was significantly lower than in 14 normal controls, although within normal limits. After thyroidectomy there was a rise in the platelet count of all of 7 patients studied. The occurrence of thrombocytopenic purpura in association with thyrotoxicosis is discussed.—*P. E. Sartwell.*

ZELLER, A.

A simple color reaction for pregnancy detection. *Naturwissensch.* 28: 712. 1940.

The diamine oxidase activity is increased in the serum of pregnant women and can be detected by the O_2 consumption of enzymic decomposition of cadaverine. Upon adding cadaverine and indigo disulfonate to the blood in question a decolorization takes place in 12 to 24 hours, if the subject is pregnant; in the absence of pregnancy or in cadaverine no color change is found in 3 days. For the reaction 1 cc. dialyzed serum is used at 38°. It is possible to use undialyzed serum, and 0.1 cc. serum is sufficient for the test.—*B. J. C. van der Hoeven.*